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☒ Additional inventors are being named on the 1 separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

CHEMICAL COMPOUNDS

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ENCLOSED APPLICATION PARTS (check all that apply)

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☐ Application Data Sheet. See 37 CFR 1.76			

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Respectfully submitted,

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Date 19 June 2003

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Docket Number: PR60317P

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Additional Page

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Docket Number	PR60317P	Type a plus sign (+) inside this box →	+

INVENTOR(S)/APPLICANT(S)

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Number 1 of 1

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60479753-061903

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **Drewry et al.**			Docket No. **PR60317P**
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Invention: **CHEMICALS COMPOUNDS**

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CHEMICAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to indazole amide derivatives, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such indazole amide derivatives are useful in the treatment of diseases associated with inappropriate tyrosine and/or serine/threonine kinase activity.

BACKGROUND OF THE INVENTION

An important large family of enzymes is the protein kinase enzyme family. Currently, there are about 500 different known protein kinases. Protein kinases serve to catalyze the phosphorylation of an amino acid side chain in various proteins by the transfer of the γ-phosphate of the ATP-Mg^{2+} complex to said amino acid side chain. These enzymes control the majority of the signaling processes inside cells, thereby governing cell function, growth, differentiation and destruction (apoptosis) through reversible phosphorylation of the hydroxyl groups of serine, threonine and tyrosine residues in proteins. Studies have shown that protein kinases are key regulators of many cell functions, including signal transduction, transcriptional regulation, cell motility, and cell division. Several oncogenes have also been shown to encode protein kinases, suggesting that kinases play a role in oncogenesis. These processes are highly regulated, often by complex intermeshed pathways where each kinase will itself be regulated by one or more kinases. Consequently, aberrant or inappropriate protein kinase activity can contribute to the rise of disease states associated with such aberrant kinase activity. Due to their physiological relevance, variety and ubiquitousness, protein kinases have become one of the most important and widely studied family of enzymes in biochemical and medical research.

The protein kinase family of enzymes is typically classified into two main subfamilies: Protein Tyrosine Kinases and Protein Serine/Threonine Kinases, based on the amino acid residue they phosphorylate. The serine/threonine kinases (PSTK), includes cyclic AMP- and cyclic GMP-dependent protein kinases, calcium- and phospholipid-dependent protein kinase, calcium- and calmodulin-dependent protein kinases, casein kinases, cell division cycle protein kinases and others. These kinases are usually cytoplasmic or associated with the particulate fractions of cells, possibly

by anchoring proteins. Aberrant protein serine/threonine kinase activity has been implicated or is suspected in a number of pathologies such as rheumatoid arthritis, psoriasis, septic shock, bone loss, many cancers and other proliferative diseases. Accordingly, serine/threonine kinases and the signal transduction pathways which they are part of are important targets for drug design. The tyrosine kinases phosphorylate tyrosine residues. Tyrosine kinases play an equally important role in cell regulation. These kinases include several receptors for molecules such as growth factors and hormones, including epidermal growth factor receptor, insulin receptor, platelet derived growth factor receptor and others. Studies have indicated that many tyrosine kinases are transmembrane proteins with their receptor domains located on the outside of the cell and their kinase domains on the inside. Much work is also under progress to identify modulators of tyrosine kinases as well.

A major signal transduction systems utilized by cells is the RhoA- signalling pathways. RhoA is a small GTP binding protein that can be activated by several extracellular stimuli such as growth factor, hormones, mechanic stress, osmotic change as well as high concentration of metabolite like glucose. RhoA activation involves GTP binding, conformation alteration, post-translational modification (geranylgeranyllization and farnesylation) and activation of its intrinsic GTPase activity. Activated RhoA is capable of interacting with several effector proteins including ROCKs and transmit signals into cellular cytoplasm and nucleus.

ROCK1 and 2 constitute a family of kinases that can be activated by RhoA-GTP complex via physical association. Activated ROCKs phosphorylate a number of substrates and play important roles in pivotal cellular functions. The substrates for ROCKs include myosin binding subunit of myosin light chain phosphatase (MBS, also named MYPT1), adducin, moesin, myosin light chain (MLC), LIM kinase as well as transcription factor FHL. The phosphorylation of theses substrates modulate the biological activity of the proteins and thus provide a means to alter cell's response to external stimuli. One well documented example is the participation of ROCK in smooth muscle contraction. Upon stimulation by phenylephrine, smooth muscle from blood vessels contracts. Studies have shown that phenylephrine stimulates b-adrenergic receptors and leads to the activation of RhoA. Activated RhoA in turn stimulates kinase activity of ROCK1 and which in turn phosphorylates MBS. Such phosphorylation inhibits the enzyme activity of myosin light chain phosphatase and

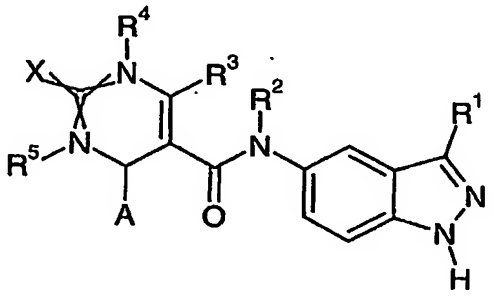
increases the phosphorylation of myosin light chain itself by a calcium-dependent myosin light chain kinase (MLCK) and consequently increases the contractility of myosin-actin bundle, leading to smooth muscle contraction. This phenomena is also sometimes called calcium sensitization. In addition to smooth muscle contraction, ROCKs have also been shown to be involved in cellular functions including apoptosis, cell migration, transcriptional activation, fibrosis, cytokinesis, inflammation and cell proliferation. Moreover, in neurons ROCK plays a critical role in the inhibition of axonal growth by myelin-associated inhibitory factors such as myelin-associated glycoprotein (MAG). ROCK-activity also mediates the collapse of growth cones in developing neurons. Both processes are thought to be mediated by ROCK-induced phosphorylation of substrates such as LIM kinase and myosin light chain phosphatase, resulting in increased contractility of the neuronal actin-myosin system.

Inhibitors of ROCKs have been suggested for use in the treatments of a variety of diseases. They include cardiovascular diseases such as hypertension, chronic and congestive heart failure, cardiac hypertrophy, restenosis, chronic renal failure and atherosclerosis. In addition, because of its muscle relaxing properties, it is also suitable for asthma, male erectile dysfunctions, female sexual dysfunction and over-active bladder syndrome. ROCK inhibitors have been shown to possess anti-inflammatory properties. Thus they can be used as treatment for neuroinflammatory diseases such as stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and inflammatory pain, as well as other inflammatory diseases such as rheumatoid arthritis, irritable bowel syndrome, inflammatory bowel disease. . In addition, based on their neurite outgrowth inducing effects, ROCK inhibitors could be useful drugs for neuronal regeneration, inducing new axonal growth and axonal rewiring across lesions within the CNS. ROCK inhibitors are therefore likely to be useful for regenerative (recovery) treatment of CNS disorders such as spinal cord injury, acute neuronal injury (stroke, traumatic brain injury), Parkinsons disease, Alzheimers disease and other neurodegenerative disorders. Since ROCK inhibitors reduce cell proliferation and cell migration, they could be useful in treating cancer and tumor metastasis. Further more, there is evidence suggesting that ROCK inhibitors suppress cytoskeletal rearrangement upon virus invasion, thus they also have potential therapeutic value in anti-viral and anti-bacterial applications. ROCK inhibitors are also useful for the treatment of insulin resistance and diabetes.

The present inventors have discovered novel indazole amide compounds, which are inhibitors of ROCK activity. Such derivatives are useful in the treatment of disorders associated with inappropriate ROCK activity.

SUMMARY OF THE INVENTION

In one aspect of the present invention, there is provided a compound of Formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

indicates a single or double bond;

X is =O, =S, C_1-C_3 alkyl, or -N(H)R;

A is aryl, aralkyl, heteroaryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl;

R is C_1-C_3 alkyl, aryl, heteroaryl, -C(O)R", -$S(O)_2$R", or -C(O)NR";

R^1 is –H, halo, C_1-C_6 alkyl, aryl, heteroaryl, or N(H)R';

R' is –H, C_1-C_3 alkyl, aryl, -C(O)R", -S(O)2R", or -C(O)N(H)R";

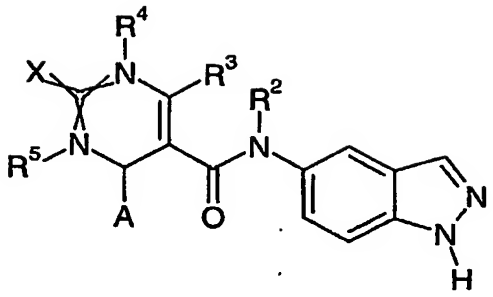
R" is C_1-C_3 alkyl;

R^2 is –H or C_1-C_3 alkyl;

R^3 is -H, C_1-C_3 alkyl, aryl or heteroaryl; and

R^4 and R^5 are each independently –H, C_1-C_3 alkyl or aralkyl.

In a second aspect of the present invention, there is provided a compound of Formula (I'):



(I')

or a salt, solvate, or physiologically functional derivative thereof:
wherein:

indicates a single or double bond;
X is =O, =S, C_1-C_3 alkyl, or -N(H)R;
A is aryl, aralkyl, heteroaryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl;
R is C_1-C_3 alkyl, aryl, heteroaryl, -C(O)R", -$S(O)_2$R", or -C(O)NR";
R' is –H, C_1-C_3 alkyl, aryl, -C(O)R", -S(O)2R", or -C(O)N(H)R";
R" is C_1-C_3 alkyl;
R^2 is –H or C_1-C_3 alkyl;
R^3 is -H, C_1-C_3 alkyl, aryl or heteroaryl; and
R^4 and R^5 are each independently –H, C_1-C_3 alkyl or aralkyl.

In a third aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a fourth aspect of the present invention, there is provided a method of treating a disorder in a mammal, said disorder being mediated by inappropriate ROCK-1 activity, comprising: administering to said mammal a therapeutically effective amount of a compound of formula (I) or a salt, solvate or a physiologically functional derivative thereof.

In a fifth aspect of the present invention, there is provided a compound of formula (I), or a salt, solvate, or a physiologically functional derivative thereof for use in therapy.

In a sixth aspect of the present invention, there is provided the use of a compound of formula (I), or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate ROCK-1 activity.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein the term "alkyl" refers to a straight- or branched-chain hydrocarbon radical having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aryl, aryloxy, heteroaryl, heterocyclyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the terms "C_1-C_3 alkyl" and "C_1-C_6 alkyl" refer to an alkyl group, as defined above, containing at least 1, and at most 3 or 6 carbon atoms respectively. Examples of such branched or straight-chained alkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, t-butyl, n-pentyl, isopentyl, and n-hexyl.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aryl, heteroaryl, heterocyclyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, and C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene, and the like.

As used herein, the term "C_1-C_3 alkylene" refers to an alkylene group, as defined above, which contains at least 1, and at most 3 or 6, carbon atoms respectively. Examples of "C_1-C_6 alkylene" and "C_1-C_6 alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene, n-propylene, n-butylene, isopentylene, and the like.

As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon-carbon double bond, optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, aryl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen and C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkenyl" as used herein include, ethenyl, propenyl, 1-butenyl, 2-butenyl, and isobutenyl.

As used herein, the term "C_1-C_6 alkenyl" refers to an alkenyl group, as defined above, containing at least 1, and at most 6, carbon atoms. Examples of "C_1-C_6 alkenyl" groups useful in the present invention include, but are not limited to, ethenyl, propenyl, 1-butenyl, 2-butenyl, and isobutenyl.

As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon-carbon triple bond, optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, aryl, hydroxy,

mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen and C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkynyl" as used herein, include but are not limited to acetylenyl, 1-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, and 1-hexynyl.

As used herein, the term "C_1-C_6 alkynyl" refers to an alkynyl group, as defined above, containing at least 1, and at most 6, carbon atoms. Examples of "C_1-C_6 alkynyl" groups useful in the present invention include, but are not limited to, to acetylenyl, 1-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, and 1-hexynyl.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo(-Br), and iodo(-I).

As used herein, the term "C_1-C_6 haloalkyl" refers to an alkyl group as defined above containing at least 1, and at most 6 carbon atoms respectively substituted with at least one halo group, halo being as defined herein. Examples of such branched or straight chained haloalkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halos, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring containing from 3 to 10 carbon atoms and which optionally includes a C_1-C_6 alkyl linker through which it may be attached. In a like manner the term "C_3-C_7 cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C_1-C_6 alkyl linker through which it may be attached. The C_1-C_6 alkyl group is as defined above. Exemplary "C_3-C_7 cycloalkyl" groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered non-aromatic heterocyclic ring, being saturated or having one or more degrees of unsaturation, containing one or more heteroatom substitutions selected from S, S(O), $S(O)_2$, O, or N, optionally substituted with

substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, aryl, aralkyl, heteroaryl, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, 2,4-piperazinedione, pyrrolidine, imidazolidine, pyrazolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene or heterocyclyl rings to form, for example, anthracene, phenanthrene, napthalene, benzodioxin ring systems. Exemplary optional substituents include C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, arylsulfonoamino, alkylcarboxy, alkylcarboxyamide, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, aryl, or heteroaryl, carboxy, tetrazolyl, carboxamide, carbamoyl optionally substituted by alkyl, aryl, or heteroaryl, aminosulfonyl, acyl, aroyl, aroylamino, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halo, heteroaryl, heterocyclyl, aryl, ureido, arylurea, alkylurea, cycloalkylurea, alkylthiourea, aryloxy, aralkoxy, or $-O(CH_2)_rOH$, where r is 1, 2, 3, or 4, multiple degrees of substitution being allowed. Examples of "aryl" groups include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, 1,4-benzodioxin-6-yl as well as substituted derivatives thereof.

As used herein, the term "aralkyl" refers to an aryl or heteroaryl group, as defined herein, attached through a C_1-C_3 alkylene linker, wherein the C_1-C_3 alkylene is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl, and 2-imidazolyl ethyl.

As used herein, the term "heteroaryl" refers to a monocyclic five to seven membered aromatic ring, or to a fused bicyclic or tricyclic aromatic ring system

comprising two of such monocyclic five to seven membered aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen heteroatoms, where N-oxides and sulfur oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, arylsulfonoamino, alkylcarboxy, alkylcarboxyamide, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, aryl, or heteroaryl, carboxy, tetrazolyl, carboxamide, carbamoyl optionally substituted by alkyl, aryl, or heteroaryl, aminosulfonyl, acyl, aroyl, aroylamino, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halo, heteroaryl, heterocyclyl, aryl, ureido, arylurea, alkylurea, cycloalkylurea, alkylthiourea, aryloxy, or aralkoxy, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, quinoxalinyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinazolinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "alkoxy" refers to the group R_aO-, where R_a is alkyl as defined above and the terms "C_1-C_3 alkoxy" and "C_1-C_6 alkoxy" refer to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1, and at most 3 or 6, carbon atoms. Exemplary "C_1-C_3 alkoxy" and "C_1-C_6 alkoxy" groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy.

As used herein, the term "amino" refers to the group $-NH_2$.

As used herein the term "alkylamino" refers to the group $-NHR_a$ wherein R_a is alkyl as defined above.

As used herein the term "arylamino" refers to the group $-NHR_a$ wherein R_a is aryl as defined above.

As used herein the term "aralkylamino" refers to the group $-NHR_a$ wherein R_a is an aralkyl group as defined above.

As used herein the term "aralkoxy" refers to the group R_bR_aO-, where R_a is alkylene and R_b is aryl or heteroaryl all as defined above.

As used herein the term "aryloxy" refers to the group R_aO-, where R_a is aryl or heteroaryl both as defined above.

As used herein the term "ureido" refers to the group $-NHC(O)NH_2$

As used herein, the term "arylurea" refers to the group $-NHC(O)NHR_aR_b$ wherein R_a is aryl or heteroaryl and R_b is –H, alkyl, or aryl as defined above.

As used herein, the term "arylthiourea" refers to the group $-NHC(S)NHR_a$ wherein R_a is aryl as defined above.

As used herein, the term "alkylurea" refers to the group $-NHC(O)NR_aR_b$ wherein R_a is alkyl and R_b is –H or alkyl as defined above.

As used herein, the term "cycloalkylurea" refers to the group $-NHC(O)NHR_a$ wherein R_a is cycloalkyl as defined above.

As used herein, the term "C_3-C_7 cycloalkoxy" refers to the group R_aO-, where R_a is C_3-C_7 cycloalkyl as defined above. Exemplary C_3-C_7 cycloalkoxy groups useful in the present invention include, but are not limited to, cyclobutoxy, and cyclopentoxy.

As used herein, the term "haloalkoxy" refers to the group R_aO-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkoxy" refers to a haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1, and at most 6, carbon atoms. Exemplary C_1-C_6 haloalkoxy groups useful in the present invention include, but is not limited to, trifluoromethoxy.

As used herein, the term "alkylsulfanyl" refers to the group R_aS-, where R_a is alkyl as defined above and the term "C_1-C_6 alkylsulfanyl" refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "haloalkylsulfanyl" refers to the group R_aS-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkylsulfanyl" refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)$-, where R_a is alkyl as defined above and the term "C_1-C_6 alkylsulfenyl" refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "alkylsulfonyl" refers to the group $R_aS(O)_2$-, where R_a is alkyl as defined above and the term "C_1-C_6 alkylsulfonyl" refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "alkylsulfonylamino" refers to the group $-NR_bS(O)_2R_a$ wherein R_a is alkyl and R_b is –H or C_1-C_6 alkyl as defined above, and the term "C_1-C_6 alkylsulfonylamino" refers to an alkylsulfonylamino group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "arylsulfonylamino" refers to the group $-NR_bS(O)_2R_a$ wherein R_a is aryl or heteroaryl and R_b is –H or C_1-C_6 alkyl as defined above.

As used herein, the term "alkylcarboxyamide" refers to the group $-NHC(O)R_a$ wherein R_a is alkyl, amino, or amino substituted with alkyl, aryl or heteroaryl as described above.

As used herein the term "alkylcarboxy" refers to the group $-C(O)R_a$ wherein R_a is alkyl as described above.

As used herein, the term "oxo" refers to the group =O.

As used herein, the term "mercapto" refers to the group -SH.

As used herein, the term "carboxy" refers to the group $-C(O)OR_a$, wherein R_a is H or alkyl as defined herein.

As used herein, the term "cyano" refers to the group -CN.

As used herein the term "cyanoalkyl" refers to the group $-R_aCN$ wherein R_a is alkyl as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl, and cyanoisopropyl.

As used herein, the term "nitro" refers to the group $-NO_2$.

As used herein, the term "aminosulfonyl" refers to the group $-S(O)_2NR_aR_b$ wherein R_a and R_b are independently H, C_1-C_6alkyl, aryl, aralkyl, or heteroaryl.

As used herein, the term "carbamoyl" refers to the group $-OC(O)NHR_a$. where R_a is hydrogen or alkyl as defined herein.

As used herein, the term "carboxamide" refers to the group $-C(O)NR_aR_b$ wherein R_a and R_b are independently H, C_1-C_6alkyl, aryl, aralkyl, or heteroaryl.

As used herein, the term "sulfanyl" shall refer to the group -S-.

As used herein, the term "sulfenyl" shall refer to the group -S(O)-.

As used herein, the term "sulfonyl" shall refer to the group $-S(O)_2-$ or $-SO_2-$.

As used herein, the term "acyl" refers to the group $R_aC(O)-$, where R_a is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyl" refers to the group $R_aC(O)-$, where R_a is aryl as defined herein.

As used herein, the term "aroylamino" refers to the group $R_aC(O)NH-$, where R_a is aryl as defined herein.

As used herein, the term "heteroaroyl" refers to the group $R_aC(O)$- , where R_a is heteroaryl as defined herein.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)$-, where R_a is alkyl as defined herein.

As used herein, the term "acyloxy" refers to the group $R_aC(O)O$- , where R_a is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O$- , where R_a is aryl as defined herein.

As used herein, the term "heteroaroyloxy" refers to the group $R_aC(O)O$- , where R_a is heteroaryl as defined herein.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable

solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

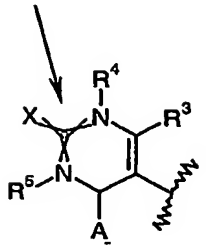
As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. The compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, it is understood that any tautomers and mixtures of tautomers of the compounds of formula (I) are included within the scope of the compounds of formula (I).

It is to be understood that reference to compounds of formula (I) and (I') above, following herein, refers to compounds within the scope of formula (I) and (I') as defined above with respect to R^1, R^2, R^3, R^4, R^5, R', R'', X, and A unless specifically limited otherwise.

In one embodiment, X is =O. In another embodiment, X is =S. In an alternative embodiment, X is C_1-C_3 alkyl, preferably $-CH_3$. In another embodiment, X is -N(H)R, where R is as defined above, preferably X is -N(H)R, where R is -H.

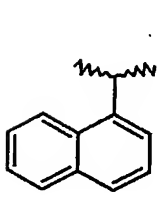
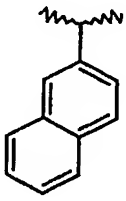
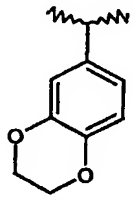
It is understood that the bonds of Formula (I), represented by  , attached to the pyrimidine ring carbon, which is between the pyrimidine nitrogens and attached to X (see arrow in formula following)

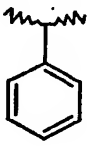


represent either single or double bonds. As is understood by those skilled in the art and specifically illustrated in the working examples following (for instance see Examples 1, 50, and 51) such bonds will independently be a single or double bond depending on which substituent of X is chosen.

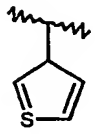
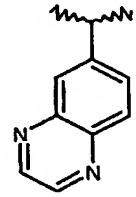
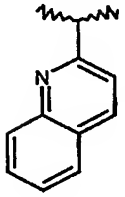
It is also understood that substituent bonding locations having an unfilled valence are indicated by "  ". The appropriate attachments are further illustrated in the working examples recited below.

In one embodiment, A is aryl. In another embodiment, A is selected from

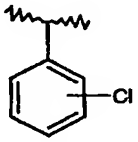
 ,  , or  .

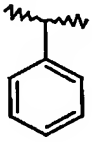
In another embodiment, A is  , optionally substituted with one or more groups selected from halo, preferably –F or -Cl; C_1-C_6 alkoxy, preferably methoxy or ethoxy; -$S(O)_2R^a$, where R^a is C_1-C_3 alkyl, preferably $–CH_3$; -$N(H)S(O)_2R^a$, where R^a is C_1-C_3 alkyl, preferably $–CH_3$; -$S(O)_2NH_2$; -$C(O)NH_2$; -C(O)OH; -CN; -OH; -$O(CH_2)_rOH$, where r is 1, 2, 3, or 4; heteroaryl, preferably  , or -$N(H)C(O)R^a$, where R^a is C_1-C_3 alkyl, preferably $–CH_3$; C_1-C_6 haloalkyl, preferably $–CF_3$.

In one embodiment, A is heteroaryl. In another embodiment, A is selected from

optionally substuted with halo, preferably –Br, or , optionally substituted with –OH.

In an alternative embodiment, A is C_1-C_6 alkyl. In another embodiment A is C_1-C_6 alkyl optionally substituted with aryl, preferably  .

In an alternative embodiment, A is C_1-C_6 alkenyl. In another embodiment A is C_1-C_6 alkenyl optionally substituted with aryl, preferably  .

In one embodiment, R^1 is –H or –N(H)R', where R' is as defined above. In one embodiment, R^1 is –H. In another embodiment, R^1 is –N(H)R', where R' is -H.

In one embodiment, R^2 is –H or C_1-C_3 alkyl. In one embodiment, R^2 is –H. In another embodiment, R^1 is C_1-C_3 alkyl, preferably methyl.

In one embodiment, R^3 is -H, C_1-C_3 alkyl, or heteroaryl. In one embodiment, R^3 is C_1-C_3 alkyl. In another embodiment, R^3 is $-CH_3$ or $-CH(CH_3)_2$. In one embodiment, R^3 is $-CH_3$. In another embodiment, R^3 is –H. In one embodiment, R^3 is heteroaryl, preferably furanyl.

As recited above R^4 and R^5 are each independently –H, C_1-C_3 alkyl or aralkyl.

In one embodiment R^4 is –H. In another embodiment, R^4 is C_1-C_3 alkyl, preferably $-CH_3$ or $-CH_2CH_3$. In another embodiment, R^4 is aralkyl, preferably benzyl.

In one embodiment R^5 is –H. In another embodiment, R^5 is C_1-C_3 alkyl, preferably $-CH_3$.

In one embodiment, A is C_1-C_6 alkenyl or C_1-C_6 alkynyl. In another embodiment, A is -CN, -COOH, or $-C(O)NR^4R^5$. In a further embodiment, A is –NRR', $-NS(O)_2R$, -NC(O)R, or $-N(R')C(O)NR^4R^5$. Wherein R, R', R^4 and R^5 are as defined above.

Specific examples of compounds of the present invention include the following:

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3,4-bis(ethyloxy)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-[4-(methylsulfonyl)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(3-thienyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-4,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(1-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(2-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-{5-[(1*H*-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoic acid;

4-(2,4-difluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-[3-(methyloxy)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-[2-(methyloxy)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-cyanophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

3-{5-[(1*H*-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoic acid;

4-(2-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-chloro-4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-{3-[(2-hydroxyethyl)oxy]phenyl}-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

4-(4-bromo-2-thienyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-hydroxyphenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-chloro-2-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-{3-[(methylsulfonyl)amino]phenyl}-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(6-quinoxalinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

4-[4-(aminosulfonyl)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(2-quinolinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3-fluoro-4-(methyloxy)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-cyanophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(1*H*-imidazol-1-yl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(3-quinolinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-[(*E*)-2-phenylethenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-chlorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[4-(acetylamino)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(2-chlorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(2,3-dihydro-1,4-benzodioxin-6-yl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-hydroxyphenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(8-hydroxy-2-quinolinyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3,4-bis(methyloxy)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[2-(4-chlorophenyl)ethyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3-(1*H*-imidazol-1-yl)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-chlorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[4-(aminocarbonyl)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-(1-methylethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-6-(2-furanyl)-*N*-1*H*-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-1,6-dimethyl-4-(2-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(2-naphthalenyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(3-thienyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1-(phenylmethyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

2-amino-4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-2,6-dimethyl-1,4-dihydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-*N*,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-N-1H-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

1-ethyl-4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide; and

N-(3-amino-1H-indazol-5-yl)-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

or a salt, solvate, or physiologically functional derivative thereof.

Further examples of compounds of the present invention include:

N-1H-indazol-5-yl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-2-oxo-4-(4-pyridinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

Methyl 3-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoate;

Methyl 4-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoate;

4-(3-furanyl)-*N*-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-4-(2-methylpropyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-2-oxo-4-(2-phenylethyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-cyano-4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluoro-3-nitrophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[2-hydroxy-4-(methyloxy)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide; and

4-(4-biphenylyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

or a salt, solvate, or physiologically functional derivative thereof.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in the compound of formula (I). Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide,

trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

While it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of the formula (I) and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula (I) and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I), or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such

formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the

compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula (I), and salts, solvates and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and

multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of formula (I) and salts, solvates and physiological functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art

having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

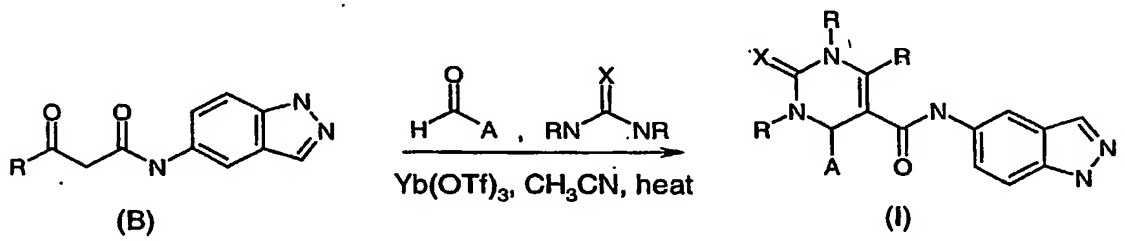
A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the human or other animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of formula (I) for the treatment of neoplastic growth, for example colon or breast carcinoma, will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the Working Examples.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the

reaction conditions and order of their execution shall be consistent with the preparation of compounds of Formula (I).

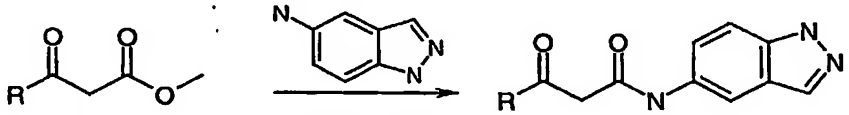
Compounds of general formula (I) can be prepared according to the synthetic sequences illustrated in Schemes 1-5 and further detailed in the Examples section following.



(B) (I)

Scheme 1

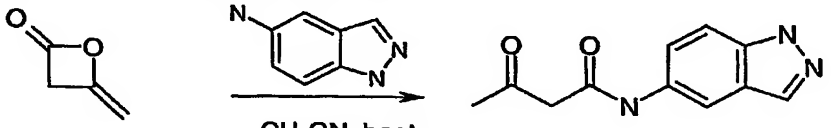
As illustrated in Scheme 1, compounds of general formula (I) may be synthesized from the beta-ketoamide (B). One way this beta-ketoamide can be converted to the pyrimidinone product is by condensation with an aldehyde and urea in an appropriate solvent at temperatures between 100 and 180 °C in the presence of an appropriate additive. For example, heating the beta-ketoamide with an aldehyde and urea in CH3CN at 100 °C in a microwave for 10 minutes, in the presence of ytterbium triflate provides the pyrimidinone (I).



(D) (B)

Scheme 2

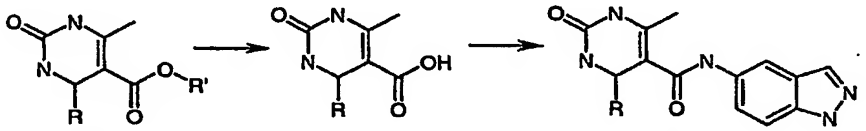
Compounds of general formula (B) can be prepared as shown in Scheme 2. For example, microwave heating of 5-aminoindazole in an excess of a beta-ketoester at 200°C for 200 seconds provides the corresponding beta-ketoamide (B). This transformation can also be accomplished by heating the reagents in an appropriate solvent, such as ethyleneglycol dimethylether.



(E) (F)

Scheme 3

Another method which can be used to generate, specifically, N-1H-indazol-5-yl-3-oxobutanamide (F) is shown in Scheme 3. This transformation involves combining 5-aminoindazole and diketene (E) in acetonitrile and heating to 50 °C in a sealed tube.

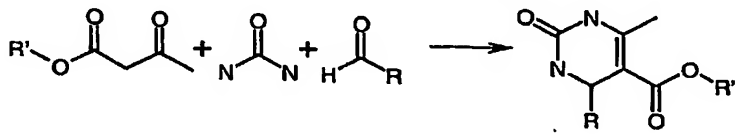


(G) (H) (I)

Scheme 4

Compounds of general formula (I) may also be synthesized from compounds of general formula (H), as depicted in Scheme 4. Compounds of general formula (H) may be synthesized from compounds of general formula (G) by conversion of the ester to a carboxylic acid. This transformation is dependent upon the type of ester used, and can be accomplished with a variety of conditions for each type of ester, examples of which can be found in the literature, specifically "Protective Groups on Organic Synthesis" by Greene and Wuts. Coupling of the resulting carboxylic acid with 5-aminoindazole provides the compound of general formula (I). This conversion from the carboxylic acid to the amide can be executed using a variety of reaction

conditions. For example, dissolving the carboxylic acid and 5-aminoindazole in dimethylformamide and heating with diisopropylethylamine, 4-(dimethylamino)-pyridine and dicyclohexylcarbodiimide provides the desired pyrimidinone (I).



(G)

Scheme 5

Compounds of formula (G) may be synthesized by reaction of a beta-ketoester, an aldehyde and urea in an appropriate solvent containing a suitable additive. There are a variety of conditions known in the chemical literature that are useful for preparing this type of compound. For example, one can combine these reagents in ethanol containing a catalytic amount of hydrochloric acid and heat to reflux for several hours. For this type of reaction, a number of catalysts, solvents, and temperature combinations have been explored and have proven useful for carrying out the desired transformation.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

EXAMPLES

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
µL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
i. v. (intravenous);	Hz (Hertz);

MHz (megaHertz); mol (moles);
mmol (millimoles); rt (room temperature);
min (minutes); h (hours);
mp (melting point); TLC (thin layer chromatography);
T_r (retention time); RP (reverse phase);
MeOH (methanol); i-PrOH (isopropanol);
TEA (triethylamine); TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran);
DMSO (dimethylsulfoxide); AcOEt (ethyl acetate);
DME (1,2-dimethoxyethane); DCM (dichloromethane);
DCE (dichloroethane); DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea); CDI (1,1'-carbonyldiimidazole);
IBCF (isobutyl chloroformate); HOAc (acetic acid);
HOSu (N-hydroxysuccinimide); HOBT (1-hydroxybenzotriazole);
mCPBA (meta-chloroperbenzoic acid);
EDC (1-[(3-dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride);
BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl);
Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);
TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); BSA (bovine serum albumin)
ATP (adenosine triphosphate); HRP (horseradish peroxidase);
DMEM (Dulbecco's modified Eagle medium);
HPLC (high pressure liquid chromatography);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
TBAF (tetra-n-butylammonium fluoride);
HBTU(O-Benzotriazole-1-yl-N,N,N',N'-tetramethyluroniumhexafluoro phosphate).
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
DPPA (diphenylphosphoryl azide);
$fHNO_3$ (fuming HNO_3); and
EDTA (ethylenediaminetetraacetic acid).

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

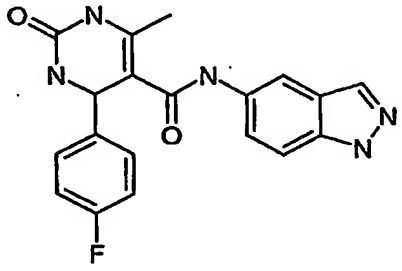
^{1}H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, a Brucker AVANCE-400, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of Hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

HPLC were recorded on a Gilson HPLC or Shimadzu HPLC system by the following conditions. Column: 50 X 4.6mm (id) stainless steel packed with 5□m Phenomenex Luna C-18 ; Flow rate: 2.0 mL/min; Mobile phase: A phase = 50mM ammonium acetate (pH 7.4), B phase = acetonitrile, 0-0.5min (A: 100%, B: 0%), 0.5-3.0 min (A:100-0%, B:0-100%), 3.0-3.5min (A: 0%, B: 100%), 3.5-3.7 min (A: 0-100%, B: 100-0%), 3.7-4.5 min (A: 100%, B: 0%); Detection : UV 254nm; Injection volume: 3□L .

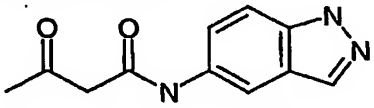
Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102, or a SCIEX-APIiii spectrometer; LC-MS were recorded on a micromass 2MD and Waters 2690; high resolution MS were obtained using a JOEL SX-102A spectrometer. All mass spectra were taken under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

Example 1

4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



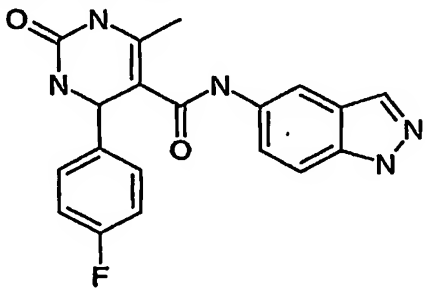
(a) *N*-1*H*-indazol-5-yl-3-oxobutanamide



In a round-bottomed flask 5-aminoindazole (500 mg, 3.75 mmol, 1 equiv) was suspended in acetonitrile (1 mL). In a separate flask, diketene (stabilized w/copper sulfate, 0.289 mL, 3.75 mmol, 1 equiv) was dissolved in acetonitrile. The diketene solution was added to the amine suspension in four portions. The reaction was sealed and heated to 50 °C for 14 h. The mixture was diluted with diethyl ether (approx. 2 mL) and the solid product was collected by filtration and washed several times with diethyl ether. The ketoamide was isolated as a white powder (761 mg, 94%).

NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 10.08 (s, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.48 (d, 1H), 7.38 (d, 1H), 3.56 (s, 2H), 2.22 (s, 3H). MS m/z 218 $(M+1)^+$.

(b) preparation of 4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



Method A: Urea (21 mg, 1.5 equiv), p-fluorobenzaldehyde (27 µL, 1.1 equiv), *N*-1*H*-indazol-5-yl-3-oxobutanamide (made in example 1(a), 50 mg, 1 equiv) and ytterbium triflate (14 mg, 0.1 equiv) were combined in acetonitrile (1 mL) and heated

to 100°C in a SmithSynthesizer for 10 minutes. The residue was diluted with 0.5 mL of water and the product was collected by filtration. The solids were washed with a 1:1 solution of acetonitrile and diethyl ether then air-dried to provide the final product (62 mg, 80%). Any products of unacceptable purity were purified further by silica gel chromatography.

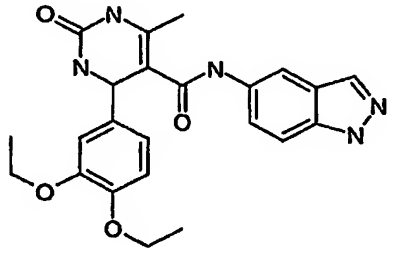
1H NMR (400 MHz, DMSO-D6) δ ppm 12.94 (s, 1H), 9.58 (s, 1H), 8.74 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.60 (s, 1H), 7.40 (m, 2H), 7.32 (m, 2H), 7.17 (m, 2H), 5.42 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 366 $[M+H]^+$

Method B: Urea (21 mg, 1.5 equiv), p-fluorobenzaldehyde (27 µL, 1.1 equiv), *N*-1*H*-indazol-5-yl-3-oxobutanamide (made in example 1(a), 50 mg, 1 equiv) and ytterbium triflate (14 mg, 0.1 equiv) were combined in acetonitrile (1 mL) and heated to 100°C in a sealed tube for three hours. The residue was diluted with 0.5 mL of water and the product was collected by filtration. The solids were washed with a 1:1 solution of acetonitrile and diethyl ether then air-dried to provide the final product (62 mg, 80%). Any products of unacceptable purity were purified further by silica gel chromatography.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.94 (s, 1H), 9.58 (s, 1H), 8.74 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.60 (s, 1H), 7.40 (m, 2H), 7.32 (m, 2H), 7.17 (m, 2H), 5.42 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 366 $[M+H]^+$

Example 2

4-[3,4-bis(ethyloxy)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

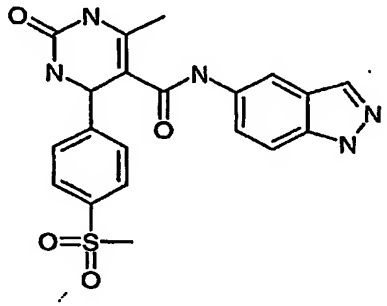


The title compound was synthesized using the procedure recited in Example 1(b), except 3,4-dimethoxybenzaldehyde was utilized.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.90 (s, 1H), 9.52 (s, 1H), 8.61 (s, 1H), 8.02 (s, 1H), 7.96 (s, 1H), 7.45 (s, 1H), 7.40 (m, 2H), 6.75-6.90 (m, 3H), 5.35 (s, 1H), 3.80-4.00 (m, 4H), 2.02 (s, 3H), 1.20-1.30 (m, 6H). MS (ES-) m/z 434.

Example 3

N-1H-indazol-5-yl-6-methyl-4-[4-(methylsulfonyl)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

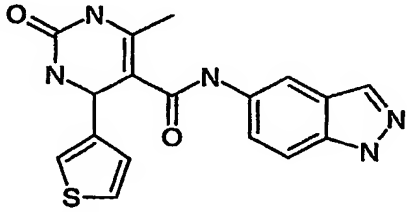


The title compound was synthesized using the procedure recited in Example 1(b), except 4-methansulfonylbenzaldehyde was utilized.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.43 (s, 1H), 8.82 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.92 (d, 2H), 7.72 (s, 1H), 7.55 (d, 2H), 7.42 (m, 2H), 5.51 (s, 1H), 3.20 (s, 3H), 2.06 (s, 3H). MS (ES+) m/e 426 $[M+H]^+$.

Example 4

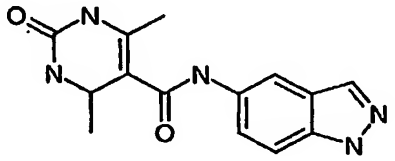
N-1H-indazol-5-yl-6-methyl-2-oxo-4-(3-thienyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-thiophenecarboxaldehyde was utilized.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.92 (s, 1H), 9.58 (s, 1H), 8.68 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.60 (s, 1H), 7.45 (m, 1H), 7.40 (s, 2H), 7.22 (s, 1H), 7.02 (m, 1H), 5.42 (s, 1H), 2.02 (s, 3H). MS (ES+) m/e 354 $[M+H]^+$.

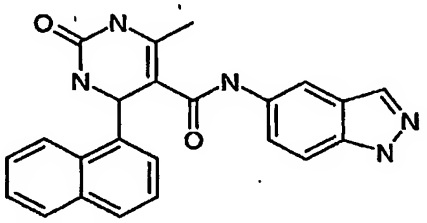
Example 5
N-1H-indazol-5-yl-4,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except acetaldehyde was utilized.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.93 (s, 1H), 9.58 (s, 1H), 8.45 (s, 1H), 8.06 (s, 1H), 7.98 (s, 1H), 7.40-7.48 (m, 2H), 7.02 (s, 1H), 4.25 (m, 1H), 1.92 (s, 3H), 1.16 (d, 3H). MS (ES+) m/e 286 $[M+H]^+$.

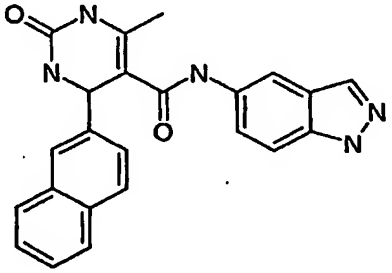
Example 6
N-1H-indazol-5-yl-6-methyl-4-(1-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 1-naphthaldehyde was utilized.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.86 (s, 1H), 9.61 (s, 1H), 8.78 (s, 1H), 8.32 (d, 1H), 7.92 (m, 3H), 7.83 (d, 1H), 7.45-7.60 (m, 5H), 7.35 (d, 1H),7.29 (d, 1H), 6.24 (s, 1H), 2.12 (s, 3H). MS (ES+) m/e 398 $[M+H]^+$.

Example 7
N-1H-indazol-5-yl-6-methyl-4-(2-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

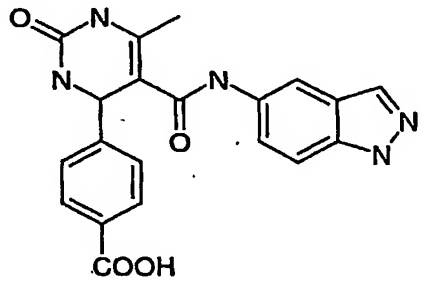


The title compound was synthesized using the procedure recited in Example 1(b), except 2-naphthaldehyde was utilized.

1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.60 (s, 1H), 8.72 (s, 1H), 7.80-8.00 (m, 5H), 7.71 (s, 1H), 7.63 (s, 1H), 7.45-7.50 (m, 3H), 7.38 (m, 2H), 5.59 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 398 $[M+H]^+$.

Example 8

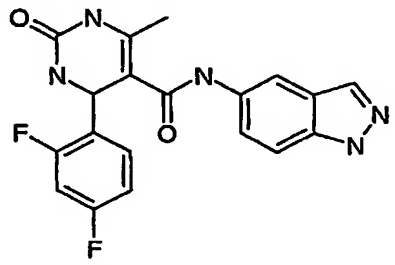
4-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoic acid



The title compound was synthesized using the procedure recited in Example 1(b), except 4-formylbenzoic acid was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.61 (s, 1H), 8.78 (s, 1H), 8.05 (d, 2H), 7.93 (d 2H), 7.71 (s, 1H), 7.45 (d, 4H), 5.5 (s, 1H), 2.12 (s, 3H). MS (ES+) m/e 392 $[M+H]^+$.

Example 9

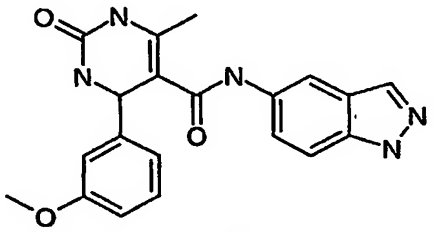
4-(2,4-difluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2,4-difluorobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.63 (s, 1H), 8.8 (s, 1H), 8 (d, 2H), 7.55 (s, 1H), 7.42 (m, 3H), 7.15 (m, 2H), 5.62 (s, 1H), 2.12 (s, 3H). MS (ES+) m/e 384 $[M+H]^+$.

Example 10

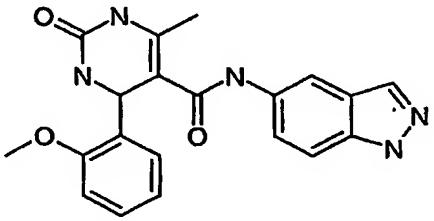
N-1H-indazol-5-yl-6-methyl-4-[3-(methyloxy)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-methoxybenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.62 (s, 1H), 8.65 (s, 1H), 8.05 (d, 2H), 7.6 (s, 1H), 7.46 (s, 2H), 7.26 (t, 1H), 6.8 (m, 3H), 5.45 (s, 1H), 3.71 (s, 3H), 2.15 (s, 3H). MS (ES+) m/e 378 $[M+H]^+$.

Example 11

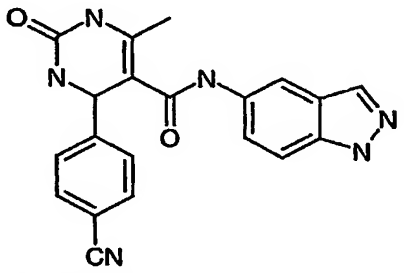
N-1H-indazol-5-yl-6-methyl-4-[2-(methyloxy)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2-methoxybenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.6 (s, 1H), 8.6 (s, 1H), 8.12 (d, 2H), 7.45 (s, 2H), 7.35 (m, 2H), 7.1 (s, 1H), 6.85 (m, 2H), 5.71 (s, 1H), 3.72 (s, 3H), 2.16 (s, 3H). MS (ES+) m/e 378 $[M+H]^+$.

Example 12

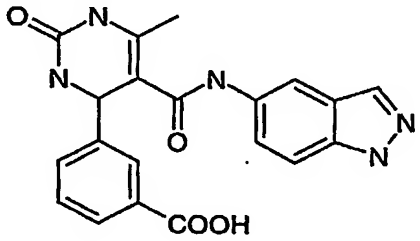
4-(4-cyanophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-cyanobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.62 (s, 1H), 8.81 (s, 1H), 8.03 (d, 2H), 7.83 (s, 1H), 7.5 (d, 2H), 7.43 (d, 2H), 5.5 (s, 1H), 2.08 (s, 3H). MS (ES+) m/e 373 $[M+H]^+$.

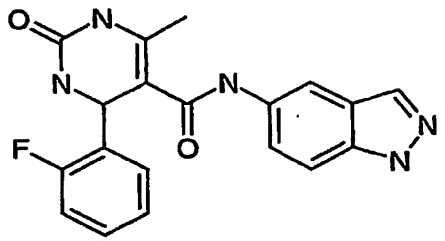
Example 13

3-[5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoic acid



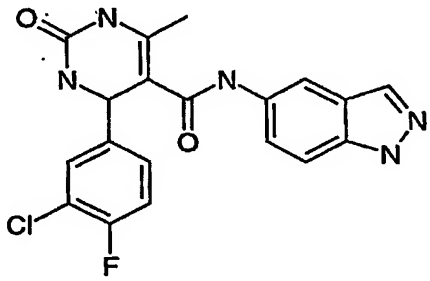
The title compound was synthesized using the procedure recited in Example 1(b), except 3-formylbenzoic acid was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 2H), 9.63 (s, 1H), 8.8 (s, 1H), 8 (m, 3H), 7.86 (d, 1H), 7.66 (s, 1H), 7.45 (m, 4H), 5.45 (s, 1H), 2.07 (s, 2H). MS (ES+) m/e 392 $[M+H]^+$.

Example 14
4-(2-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2-fluorobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (s, 1H), 9.65 (s, 1H), 8.77 (s, 1H), 8 (d, 2H), 7.53 (s, 1H), 7.4 (m, 3H), 7.3 (m, 1H), 7.15 (m, 2 H), 5.66 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 366 $[M+H]^+$.

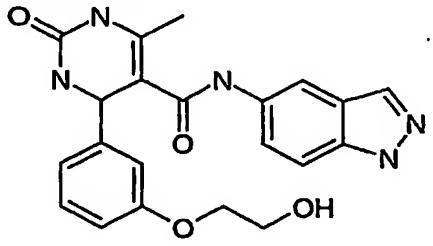
Example 15
4-(3-chloro-4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-chloro-4-fluorobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.9 (s, 1H), 9.6 (s, 1H), 8.82 (s, 1H), 8.02 (d, 2H), 7.66 (s, 1H), 7.45 (m, 4H), 7.32 (m, 1H), 5.42 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 400 $[M+H]^+$.

Example 16

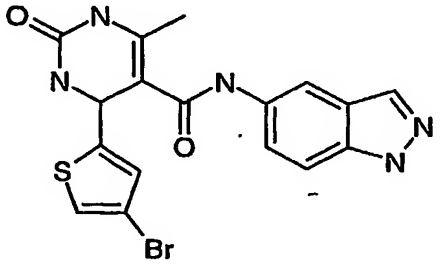
4-{3-[(2-hydroxyethyl)oxy]phenyl}-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-[(2-hydroxyethyl)oxy]benzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.6 (s, 1H), 8.65 (s, 1H), 8.02 (d, 2H), 7.6 (s, 1H), 7.4 (s, 2H), 7.22 (t, 1H), 7.82 (m, 3H), 5.41 (s, 1H), 4.85 (t, 1H), 3.86 (t, 2H), 3.65 (t, 2H), 2.05 (s, 3H). MS (ES+) m/e 408 $[M+H]^+$.

Example 17

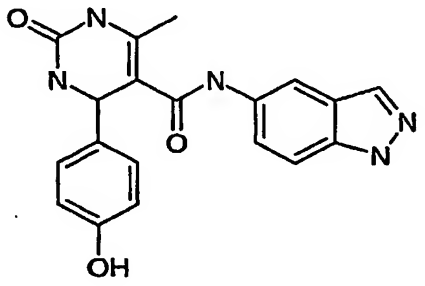
4-(4-bromo-2-thienyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-bromo-2-thiophenecarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.9 (s, 1H), 9.6 (s, 1H), 8.89 (s, 1H), 8.06 (d, 2H), 7.83 (s, 1H), 7.6 (s, 1H), 7.45 (s, 2H), 6.95 (s, 1H), 5.65 (s, 1H), 2.1 (s, 3H). MS (ES+) m/e 433 $[M+H]^+$.

Example 18

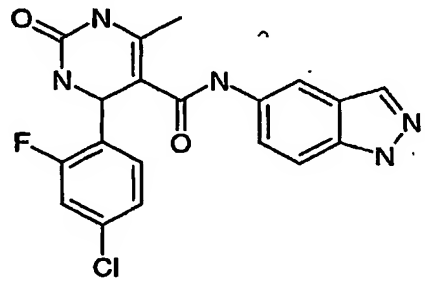
4-(4-hydroxyphenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-hydroxybenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 9.45 (s, 1H), 9.34 (s, 1H), 8.64 (s, 1H), 8.06 (d, 2H), 7.45 (d, 3H), 7.22 (d, 2H), 6.73 (d, 2H), 5.32 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 364 $[M+H]^+$.

Example 19

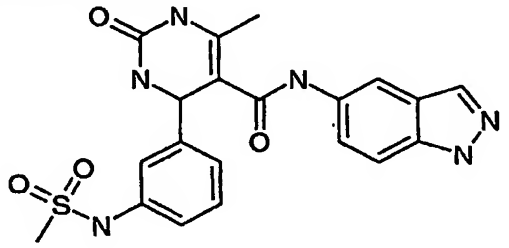
4-(4-chloro-2-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2-fluoro-4-chlorobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.64 (s, 1H), 8.82 (s, 1H), 8 (d, 2H), 7.57 (s, 1H), 7.4 (s, 5H), 5.61 (s, 1H), 2.02 (s, 3H). MS (ES+) m/e 400 $[M+H]^+$.

Example 20

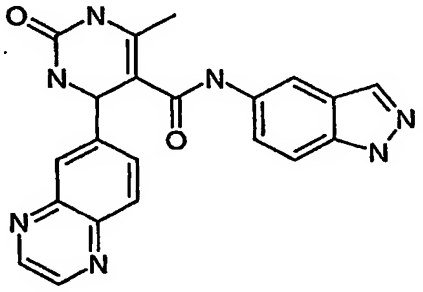
N-1H-indazol-5-yl-6-methyl-4-{3-[(methylsulfonyl)amino]phenyl}-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except *N*-(3-formylphenyl)methanesulfonamide was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.79 (s, 1H), 9.6 (s, 1H), 8.75 (s, 1H), 8 (d, 2H), 7.6 (s, 1H), 7.43 (s, 2H), 7.3 (t, 2H), 7.2 (s, 1H), 7.08 (t, 2H), 5.41 (s, 1H), 2.9 (s, 3H), 2.05 (s, 3H). MS (ES+) m/e 441 $[M+H]^+$.

Example 21

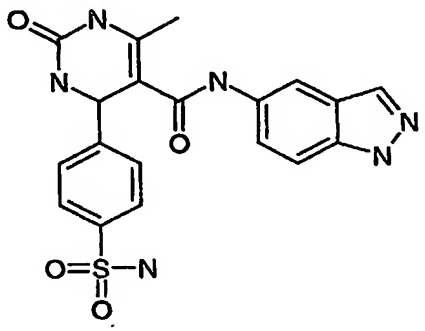
N-1H-indazol-5-yl-6-methyl-2-oxo-4-(6-quinoxalinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 6-quinoxalinecarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.7 (s, 1H), 8.95 (d, 2H), 8.9 (s, 1H), 8.14 (d, 1H), 8.04 (s, 1H), 7.97 (d, 2H), 7.86 (m, 2H), 7.43 (s, 2H), 5.7 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 400 $[M+H]^+$.

Example 22

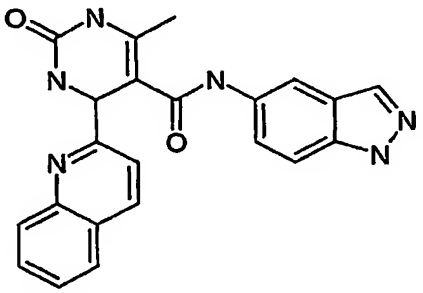
4-[4-(aminosulfonyl)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-formylbenzenesulfonamide was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.65 (s, 1H), 8.82 (s, 1H), 8.02 (d, 2H), 7.82 (d, 2H), 7.69 (s, 1H), 7.46 (m, 4H), 7.32 (s, 2H), 5.5 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 427 $[M+H]^+$.

Example 23

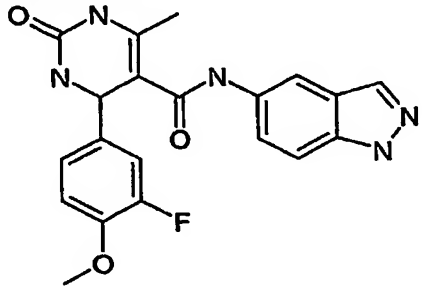
N-1H-indazol-5-yl-6-methyl-2-oxo-4-(2-quinolinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2-quinolinecarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 10.08 (s, 1H), 8.95 (s, 1H), 8.55 (d, 1H), 8.1 (s, 1H), 8.09 (m, 3H), 7.83 (t, 2H), 7.63 (m, 2H), 7.48 (s, 2H), 5.63 (s, 1H), 2.11 (s, 3H). MS (ES+) m/e 399 $[M+H]^+$.

Example 24

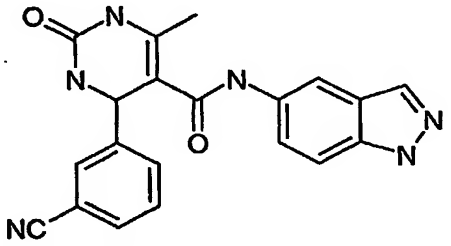
4-[3-fluoro-4-(methyloxy)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-fluoro-4-methoxybenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.59 (s, 1H), 8.74 (s, 1H), 8.03 (d, 2H), 7.59 (s, 1H), 7.44 (s, 1H), 7.29 (s, 1H), 7.13 (m, 2H), 6.95 (s, 1H), 5.39 (s, 1H), 3.82 (s, 3H), 2.1 (s, 3H). MS (ES+) m/e 396 $[M+H]^+$.

Example 25

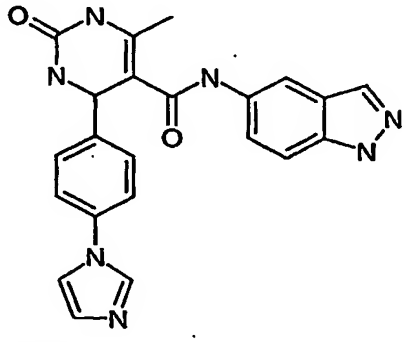
4-(3-cyanophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-cyanobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.97 (s, 1H), 9.65 (s, 1H), 8.86 (s, 1H), 8.01 (s, 2H), 7.67 (m, 5H), 7.42 (m, 2H), 5.47 (s, 1H), 2.11 (s, 3H). MS (ES+) m/e 373 $[M+H]^+$.

Example 26

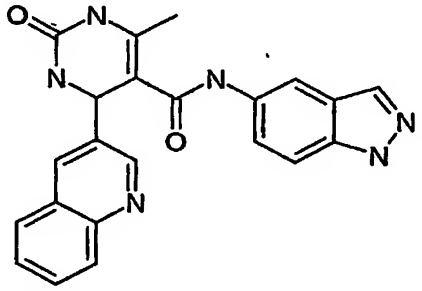
4-(1H-imidazol-1-yl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-(1*H*-imidazol-1-yl)benzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (br s, 1H), 9.68 (s, 1H), 9.63 (s, 1H), 8.85 (s, 1H), 8.26 (s, 1H), 8.07 (s, 1H), 8.01 (s, 1H), 7.91 (s, 1H), 7.78 (d, 2H), 7.74 (s, 1H), 7.56 (d, 2H), 7.46 (s, 2H), 5.55 (s, 1H), 2.13 (s, 3H). MS (ES+) m/e 414 $[M+H]^+$.

Example 27

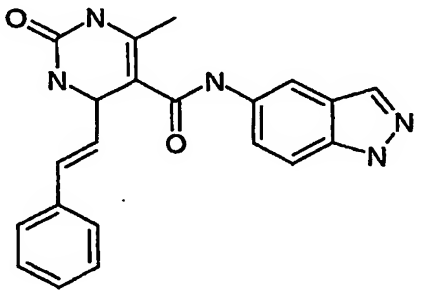
N-1H-indazol-5-yl-6-methyl-2-oxo-4-(3-quinolinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-quinolinecarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 9.73 (s, 1H), 9.05 (s, 1H), 8.97 (s, 1H), 8.47 (s, 1H), 8.15 (m, 2H), 8 (d, 2H), 7.9 (t, 1H), 7.8 (s, 1), 7.65 (t, 1H), 7.4 (m, 3H), 5.69 (s, 1H), 2.16 (s, 3H). MS (ES+) m/e 399 $[M+H]^+$.

Example 28

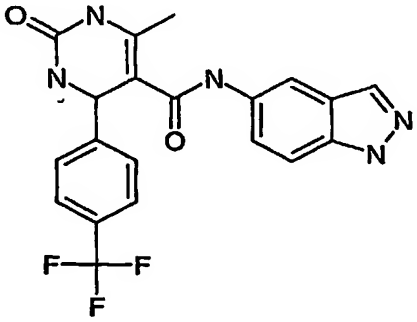
N-1H-indazol-5-yl-6-methyl-2-oxo-4-[(E)-2-phenylethenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except (2*E*)-3-phenyl-2-propenal was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (br s, 1H), 9.63 (s, 1H), 8.69 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.48 (s, 1H), 7.41 (d, 2H), 7.3 (m, 5H), 6.46 (d (1H), 6.29 (d, 1H), 4.95 (s, 1H), 2.06 (s, 3H). MS (ES+) m/e 374 $[M+H]^+$.

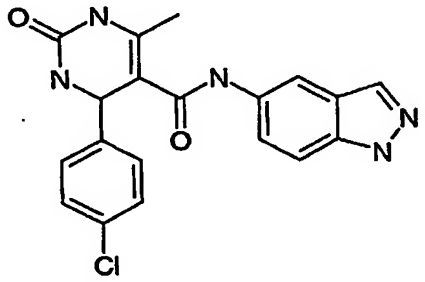
Example 29

N-1H-indazol-5-yl-6-methyl-2-oxo-4-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



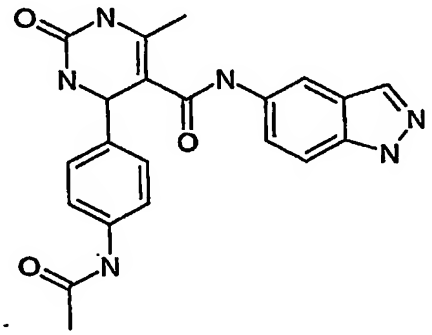
The title compound was synthesized using the procedure recited in Example 1(b), except 4-trifluoromethylbenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.65 (s, 1H), 8.82 (s, 1H), 8.04 (d, 2H), 7.76 (d, 2H), 7.7 (s, 1H), 7.54 (d, 2H), 7.44 (d, 2H), 5.52 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 416 $[M+H]^+$.

Example 30
4-(4-chlorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



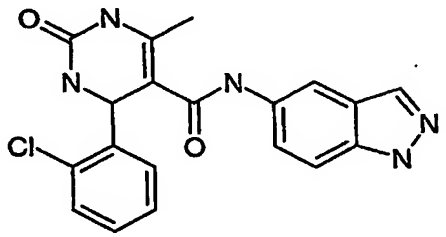
The title compound was synthesized using the procedure recited in Example 1(b), except 4-chloro-benzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.6 (s, 1H), 8.8 (s, 1H), 8 (d, 2H), 7.6 (s, 1H), 7.4 (d, 4H), 7.3 (d, 2H), 5.4 (s, 1H), 2.05 (s, 3H). MS (ES+) m/e 382 $[M+H]^+$.

Example 31
4-[4-(acetylamino)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



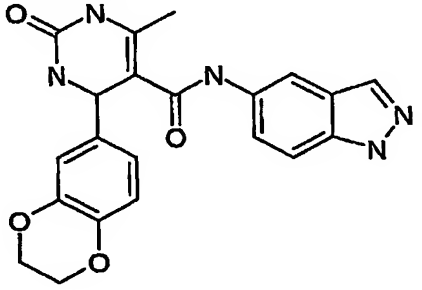
The title compound was synthesized using the procedure recited in Example 1(b), except N-(4-formylphenyl)-acetamide was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.93 (s, 1H), 9.55 (s, 1H), 8.68 (s, 1H), 8.01 (d, 2H), 7.47 (m, 5H), 7.23 (d, 2H), 5.39 (s, 1H), 2.06 (s, 3H), 2.03 (s, 3H). MS (ES+) m/e 405 $[M+H]^+$.

Example 32
4-(2-chlorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



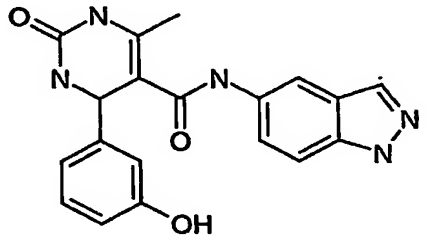
The title compound was synthesized using the procedure recited in Example 1(b), except 2-chlorobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.88 (br s, 1H), 9.7 (s, 1H), 8.78 (s, 1H), 8 (d, 2H), 7.53 (d, 2H), 7.4 (m, 4H), 7.28 (m, 1H), 5.84 (s, 1H), 2.08 (s, 3H). MS (ES+) m/e 383 $[M+H]^+$.

Example 33
4-(2,3-dihydro-1,4-benzodioxin-6-yl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



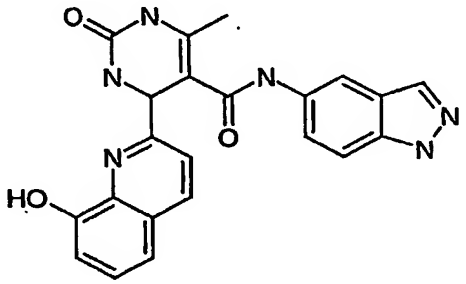
The title compound was synthesized using the procedure recited in Example 1(b), except 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.97 (s, 1H), 9.56 (s, 1H), 8.68 (s, 1H), 8.03 (s, d, 2H), 7.5 (s, 1H), 7.45 (s, 2H), 6.79 (m, 3 H), 5.35 (s, 1H), 4.22 (s, 3H), 2.09 (s, 3H). MS (ES+) m/e 406 $[M+H]^+$.

Example 34
4-(3-hydroxyphenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-hydroxybenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.57 (s, 1H), 9.4 (s, 1H), 8.68 (s, 1H), 8.04 (d, 2H), 7.54 (s, 1H), 7.45 (s, 2H), 7.12 (t, 1H), 6.69 (m, 3H), 5.38 (s, 1H), 2.07 (s, 3H). MS (ES+) m/e 364 $[M+H]^+$.

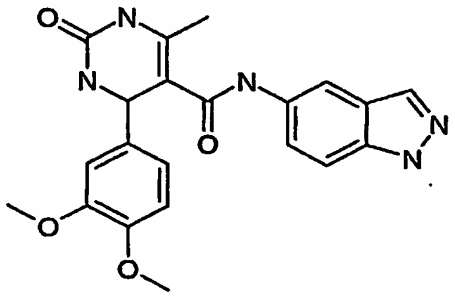
Example 35
4-(8-hydroxy-2-quinolinyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 8-hydroxy-2-quinolinecarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.9 (br s, 1H), 10.21 (s, 1H), 9.89 (br s, 1H), 9.02 (s, 1H), 8.51 (d, 1H), 8.14 (s, 1H), 8 (s, 1H), 7.65 (d, 1H), 7.5 (d, 1H), 7.48 (t, 2H), 7.2 (d, 3H), 5.64 (s, 1H), 2.14 (s, 3H). MS (ES+) m/e 415 $[M+H]^+$.

Example 36

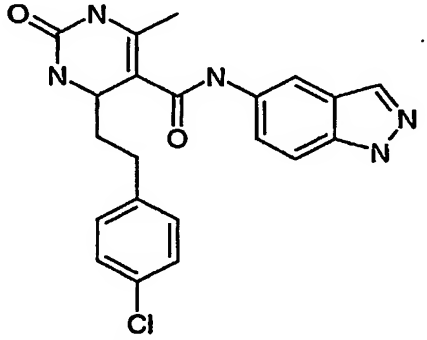
4-[3,4-bis(methyloxy)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3,4-dimethoxybenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.57 (s, 1H), 8.67 (s, 1H), 8.03 (d, 2H), 7.52 (s, 1H), 7.45 (s, 2H), 6.89 (m, 3H), 5.42 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.08 (s, 3H). MS (ES+) m/e 409 $[M+H]^+$.

Example 37

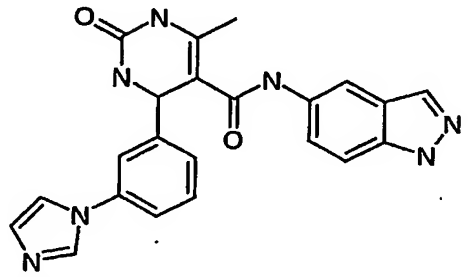
4-[2-(4-chlorophenyl)ethyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-(4-chlorophenyl)propanal was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 9.66 (s, 1H), 8.53 (s, 1H), 8.07 (d, 2H), 7.48 (s, 2H), 7.26 (m, 5H), 4.31 (s, 1H), 2.75 (t, 2H), 2.01 (s, 3H), 1.77 (t, 2H). MS (ES+) m/e 409 $[M+H]^+$.

Example 38

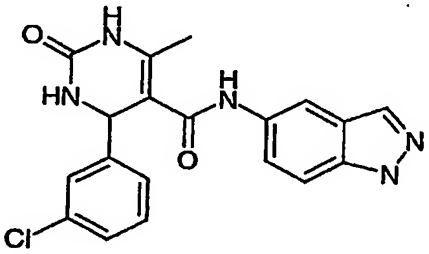
4-[3-(1H-imidazol-1-yl)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-(1*H*-imidazol-1-yl)benzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.99 (s, 1H), 9.68 (s, 1H), 9.39 (s, 1H), 8.83 (s, 1H), 8.13 (d, 1H), 8.01 (d, 2H), 7.81 (s, 1H), 7.64 (m, 4H), 7.52 (m, 1H), 7.42 (m, 2H), 5.52 (s, 1H), 2.13 (s, 3H). MS (ES+) m/e 414 $[M+H]^+$.

Example 39

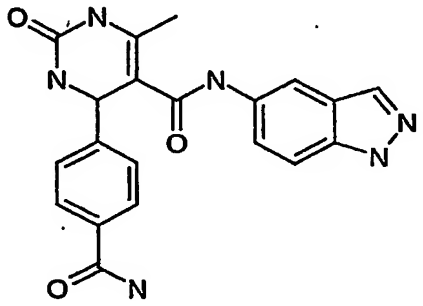
4-(3-chlorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-formylbenzamide was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.63 (s, 1H), 8.61 (s, 1H), 8.05 (d, 2H), 7.65 (s, 1H), 7.45 (m, 5H), 7.25 (d, 1H), 5.4 (s, 1H), 2.09 (s, 3H). MS (ES+) m/e 383 $[M+H]^+$.

Example 40

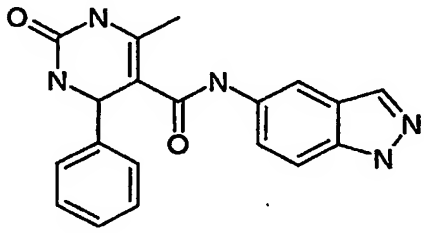
4-[4-(aminocarbonyl)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-formylbenzamide was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.63 (s, 1H), 8.77 (s, 1H), 8.05 (d, 2H), 7.95 (d, 2H), 7.65 (s, 1H), 7.4 (m, 4H), 5.5 (s, 1H), 3.58 (s, 2H), 2.09 (s, 3H). MS (ES+) m/e 391 $[M+H]^+$.

Example 41

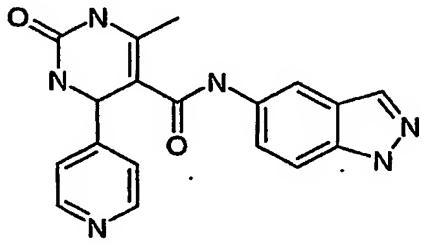
N-1H-indazol-5-yl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except benzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.6 (s, 1H), 8.72 (s, 1H), 8.02 (d, 2H), 7.6 (s, 1H), 7.44 (s, 2H), 7.34 (m, 5H), 5.46 (s, 1H), 2.09 (s, 3H). MS (ES+) m/e 348 $[M+H]^+$.

Example 42

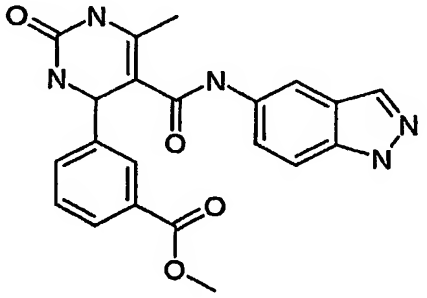
N-1H-indazol-5-yl-6-methyl-2-oxo-4-(4-pyridinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-pyridyl aldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.7 (s, 1H), 8.87 (s, 1H), 8.58 (d, 2H), 8.03 (d, 2H), 7.76 (s, 1H), 7.45 (m, 2H), 7.35 (d, 2H), 5.44 (s, 1H), 2.1 (s, 3H). MS (ES+) m/e 349 $[M+H]^+$.

Example 43

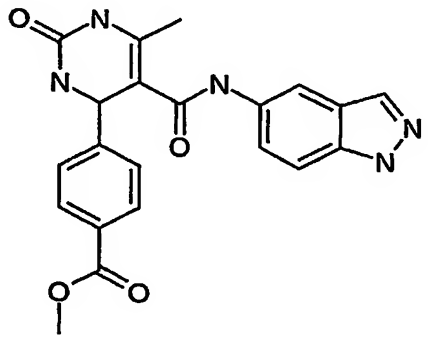
Methyl 3-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoate



The title compound was synthesized using the procedure recited in Example 1(b), except methyl 3-formylbenzoate was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.97 (s, 1H), 9.63 (s, 1H), 8.81 (s, 1H), 7.99 (d, 3H) 7.87 (d, 1H), 7.69 (s, 1H), 7.52 (m, 4H), 5.53 (s, 1H), 3.37 (s, 3H), 2.1 (s, 3H). MS (ES+) m/e 406 $[M+H]^+$.

Example 44

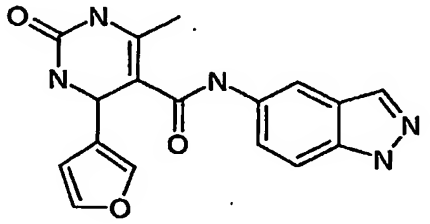
Methyl 4-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoate



The title compound was synthesized using the procedure recited in Example 1(b), except methyl 4-formylbenzoate was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.63 (s, 1H), 8.8 (s, 1H), 7.99 (m, 4H), 7.69 (s, 1H), 7.44 (m, 4H), 5.52 (s, 1H), 3.85 (s, 3H), 2.09 (s, 3H). MS (ES+) m/e 406 $[M+H]^+$.

Example 45

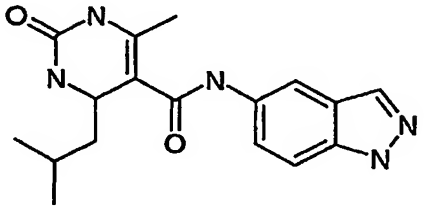
4-(3-furanyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-furancarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.95 (br s, 1H), 9.58 (s, 1H), 8.7 (s, 1H), 8.04 (d, 2H), 7.61 (s, 1H), 7.5 (m, 4H), 6.45 (s, 1H), 5.36 (s, 1H), 2.08 (s, 3H). MS (ES+) m/e 338 $[M+H]^+$.

Example 46

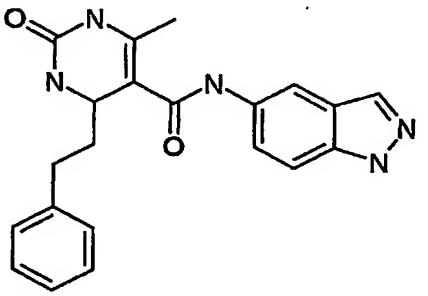
N-1H-indazol-5-yl-6-methyl-4-(2-methylpropyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-methylbutanal was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13.32 (br s, 1H), 9.64 (s, 1H), 8.49 (s, 1H), 8.08 (d, 2H), 7.49 (s, 2H), 7.25 (s, 1H), 4.26 (s, 1H), 2.01 (s, 3H), 1.78 (m, 1H), 1.35 (m, 2H), 0.87 (d, 6H). MS (ES+) m/e 328 $[M+H]^+$.

Example 47

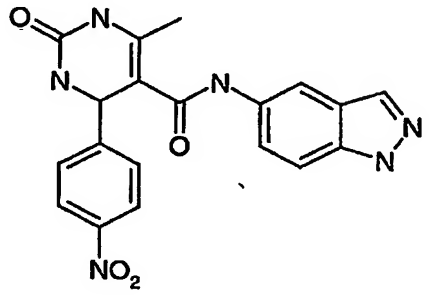
N-1H-indazol-5-yl-6-methyl-2-oxo-4-(2-phenylethyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-phenylpropanal was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 9.68 (s, 1H), 8.52 (s, 1H), 8.07 (d, 2H), 7.49 (s, 2H), 7.23 (m, 6H), 4.25 (s, 1H), 3.36 2.53 (t, 4H), 2.02 (s, 3H). MS (ES+) m/e 376 $[M+H]^+$.

Example 48

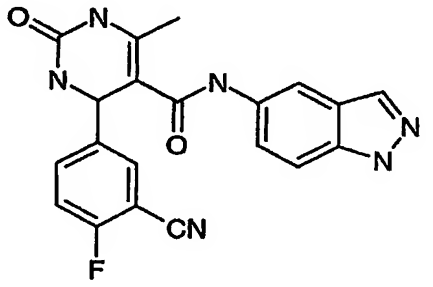
N-1H-indazol-5-yl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-nitrobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.97 (s, 1H), 9.67 (s, 1H), 8.89 (s, 1H), 8.26 (d, 2H), 8.02 (d, 2H), 7.78 (s, 1H), 7.58 (d, 2H) 7.43 (m, 2H), 5.56 (s, 1H), 2.1 (s, 3H). MS (ES+) m/e 393 $[M+H]^+$.

Example 49

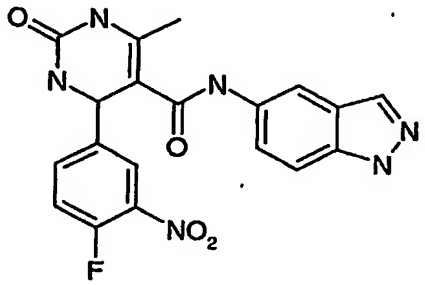
4-(3-cyano-4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2-fluoro-5-formylbenzonitrile was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 9.65 (s, 1H), 8.89 (s, 1H), 8.01 (s, 2H), 7.81 (d, 1H), 7.75 (m, 1H), 7.69 (s, 1H), 7.57 (t, 1H), 7.42 (m, 2H), 5.44 (s, 1H), 2.12 (s, 3H). MS (ES+) m/e 391 $[M+H]^+$.

Example 50

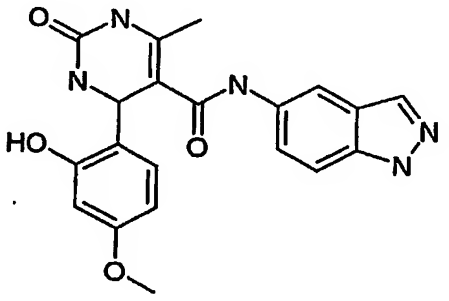
4-(4-fluoro-3-nitrophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 4-fluoro-3-nitrobenzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 9.67 (s, 1H), 8.93 (s, 1H), 8.05 (m, 3H), 7.75 (m, 2H), 7.63 (m, 1H), 7.42 (m, 2H), 5.51 (s, 1H), 2.13 (s, 3H). MS (ES+) m/e 411 $[M+H]^+$.

Example 51

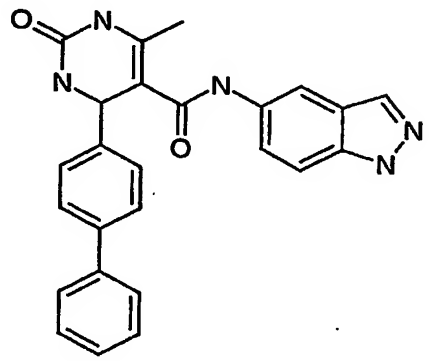
4-[2-hydroxy-4-(methyloxy)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2-hydroxy-4-(methyloxy)benzaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 13.01 (s, 1H), 10.18 (s, 1H), 8.18 (s, 1H), 8.04 (s, 1H), 7.52 (d, 2H), 7.43 (d, 1H), 7.12 (m, 2H), 6.55 (d, 1H), 6.42 (d, 1H), 4.53 (s, 1H), 3.74 (s, 3H), 3.17 (s, 1H), 1.76 (s, 3H). MS (ES+) m/e 394 $[M+H]^+$.

Example 52

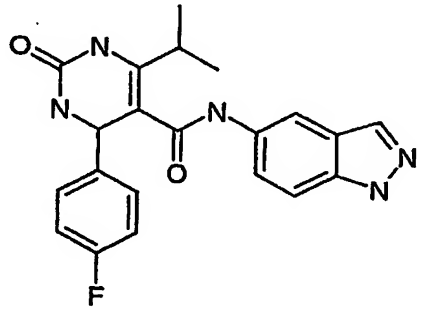
4-(4-biphenylyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



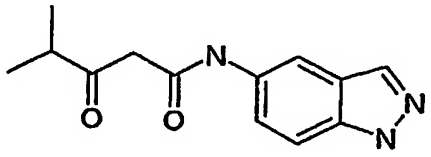
The title compound was synthesized using the procedure recited in Example 1(b), except 4-biphenylcarbaldehyde was utilized. 1H NMR (400 MHz, DMSO-D6) δ ppm 12.96 (s, 1H), 9.65 (s, 1H), 8.76 (s, 1H), 8.05 (d, 2H), 7.66 (m, 5H) 7.42 (M, 7H), 5.51 (s, 1H), 2.11 (s, 3H). MS (ES+) m/e 424 $[M+H]^+$.

Example 53

4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-(1-methylethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



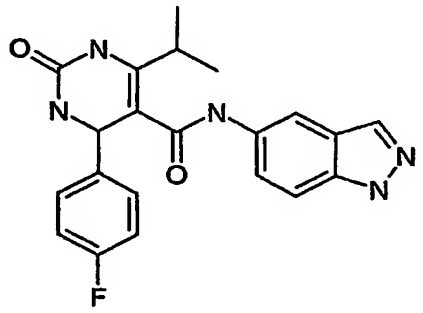
(a) *N*-1*H*-indazol-5-yl-4-methyl-3-oxopentanamide



Methyl isobutyrylacetate (3 mL) was mixed with 5-aminoindazole (0.50 g) and heated in a SmithSynthesizer to 180°C for 300 seconds. The crude mixture was then purified by silica gel chromatography to yield the title compound as a purple solid. 1H

NMR (keto- tautomer) (400 MHz, DMSO-D6) δ ppm 12.98 (s, 1H), 10.06 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.48 (d, 1H), 7.38 (d, 1H), 3.62 (s, 2H), 2.78 (sept, 1H), 1.06 (d, 6H). MS m/z 246 $(M+1)^+$.

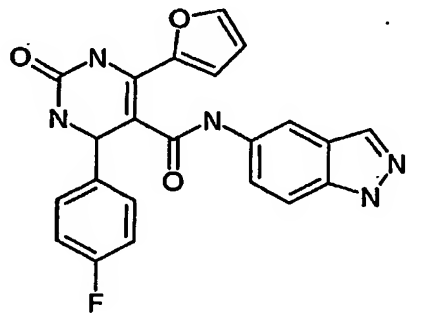
(b) 4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-(1-methylethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



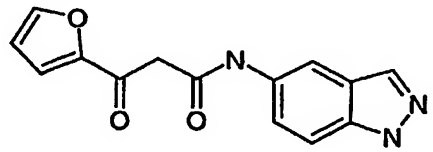
The title compound was synthesized using the procedure recited in Example 1(b), except *N*-1*H*-indazol-5-yl-4-methyl-3-oxopentanamide was utilized. NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.8 (s, 1H), 8.5 (s, 1H), 8 (s, 2H), 7.58 (s, 1H), 7.44 (d, 1H), 7.35 (m, 3H), 7.2 (t, 2H), 5.4 (s, 1H), 3.2 (m, 1H),1.1 (d, 3H), 1.06 (d, 3H). MS m/z 394 $(M+1)^+$.

Example 54

4-(4-fluorophenyl)-6-(2-furanyl)-N-1H-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

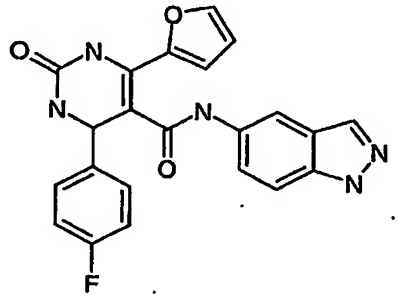


(a) 3-(2-furanyl)-*N*-1*H*-indazol-5-yl-3-oxopropanamide



Ethyl 2-(fur-2-oyl)acetate (3 mL) was mixed with 5-aminoindazole (0.50 g) and heated in a SmithSynthesizer to 180°C for 300 seconds. The crude mixture was then purified by silica gel chromatography to yield the title compound as a light purple solid. 1H NMR (keto tautomer) (400 MHz, DMSO-D6) δ ppm 12.99 (s, 1H), 10.22 (s, 1H), 8.11 (s, 1H), 8.05 (s, 1H), 8.02 (s, 1H), 7.58 (d, 1H), 7.49 (d, 1H), 7.40 (dd, 1H), 6.77 (dd, 1H), 3.96 (s, 2H). MS m/z 270 $(M+1)^+$.

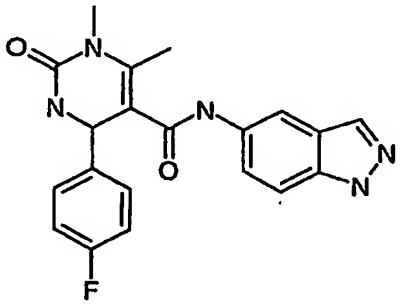
(b) 4-(4-fluorophenyl)-6-(2-furanyl)-*N*-1*H*-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 3-(2-furanyl)-*N*-1*H*-indazol-5-yl-3-oxopropanamide was utilized. NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 13 (s, 1H), 9.8 (s, 1H), 8.8 (s, 1H), 8 (d, 2H), 7.7 (d, 2H), 7.4 (m, 3H), 7.2 (m, 3H), 6.95 (d, 1H), 6.5 (d, 1H), 5.3 (s, 1H). MS m/z 418 $(M+)^+$.

Example 55

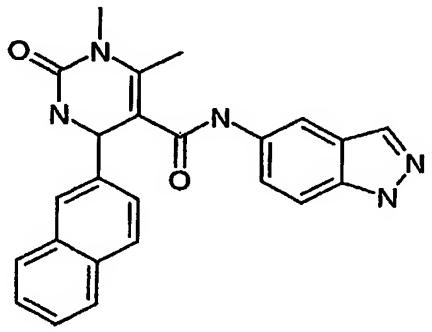
4-(4-fluorophenyl)-N-1H-indazol-5-yl-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2.0 equivalents of N-methylurea and 1.5 equivalents of 4-fluorobenzaldehyde were used to yield 64 mg (74%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 12.95 (s, 1H), 9.83 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.75 (d, 1H, 3.03 Hz), 7.42-7.44 (m, 2H), 7.29-7.33 (m, 2H), 7.14-7.19 (m, 2H), 3.09 (s, 3H), 2.19 (s, 3H). MS (ES+) m/e 380 $[M+H]^+$.

Example 56

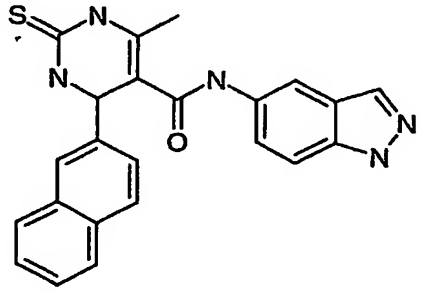
N-1H-indazol-5-yl-1,6-dimethyl-4-(2-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2.0 equivalents of N-methylurea and 1.0 equivalents of 2-naphthaldehyde were used. The title compound was triturated with CH_2Cl_2 to yield 127 mg (67%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 12.94 (s, 1H), 9.87 (s, 1H), 8.04 (s, 1H), 7.97 (s, 1H), 7.82-7.91 (m, 4H), 7.72 (s, 1H), 7.41-7.50 (m, 5H), 5.49 (s, 1H), 3.13 (s, 3H), 2.21 (s, 3H). MS (ES+) m/e 412 $[M+H]^+$.

Example 57

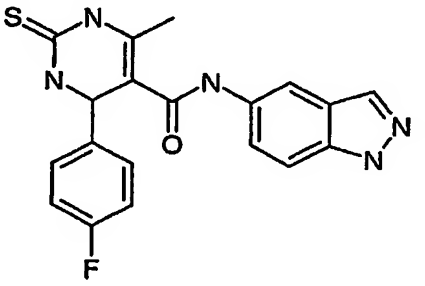
N-1H-indazol-5-yl-6-methyl-4-(2-naphthalenyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 1.0 equivalents of 2-naphthaldehyde, 0.05 equivalents of ytterium triflate and thiourea were used. The title compound was purified by RP-HPLC (retention time 8.12 min, 0-80% CH_3CN/H_2O/0.1% TFA over 10 minutes) to yield 30 mg (32%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 10.04 (s, 1H), 9.78 (s, 1H), 9.52 (s, 1H), 7.87-8.01 (m, 5H), 7.73 (s, 1H), 7.37-7.53 (m, 5H), 5.58-5.60 (m, 2H), 2.12 (s, 3H). MS (ES+) m/e 414 $[M+H]^+$.

Example 58

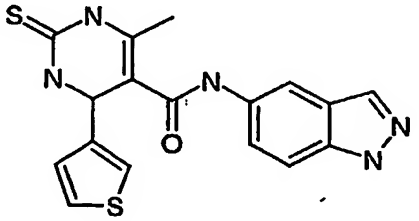
4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except thiourea was used in place of urea and 1.0 equivalent of 4-fluorobenzaldehyde was used to yield 650 mg (81%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 10.03 (s, 1H), 9.75 (s, 1H), 9.45 (s, 1H), 8.01 (d, 2H, 12.88Hz), 7.40-7.46 (m, 2H), 7.30-7.33 (m, 2H), 7.18-7.23 (m, 2H), 5.42 (d, 1H, 8.85Hz), 2.10 (s, 3H). MS (ES+) m/e 382 $[M+H]^+$.

Example 59

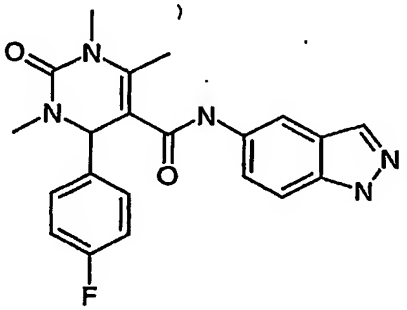
N-1H-indazol-5-yl-6-methyl-4-(3-thienyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except 2.0 equivalents of thiourea, 1.5 equivalents of 3-thiophenecarboxaldehyde and 0.05 equivalents of ytterbium triflate were used. The title compound was purified by RP-HPLC (retention time 7.20 min, 0-80% CH_3CN/H_2O/0.1% TFA over 10 minutes) to yield 2 mg (1%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 10.00 (s, 1H), 9.75 (s, 1H), 9.49 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.52-7.54 (m, 1H), 7.42-7.47 (m, 2H), 7.29 (d, 1H, 2.53Hz), 7.06 (dd, 1H, 1.26Hz, 5.05Hz), 5.45 (d, 1H, 3.03Hz), 2.10 (s, 3H). MS (ES+) m/e 370 $[M+H]^+$.

Example 60

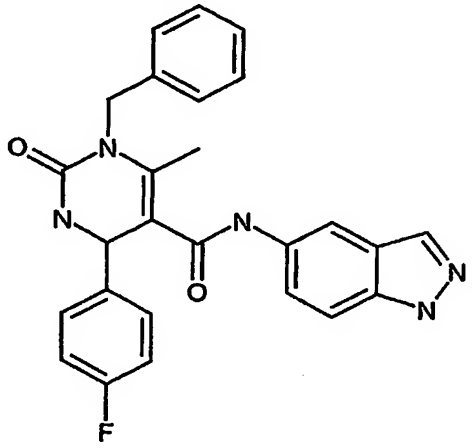
4-(4-fluorophenyl)-N-1H-indazol-5-yl-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except N,N'-dimethylurea was used in place of urea, 1.0 equivalent of 4-fluorobenzaldehyde was used, and 0.05 equivalents of ytterbium triflate were used. The title compound was purified by RP-HPLC (retention time 7.69 min, 0-80% CH_3CN/H_2O/0.1% TFA over 10 minutes) to yield 14 mg (8%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 9.82 (s, 1H), 8.05 (s, 1H), 8.00 (s, 1H), 7.39-7.47 (m, 2H), 7.17-7.27 (m, 4H), 5.34 (s, 1H), 3.15 (s, 3H), 2.79 (s, 3H), 2.17 (s, 3H). MS (ES+) m/e 394 $[M+H]^+$.

Example 61

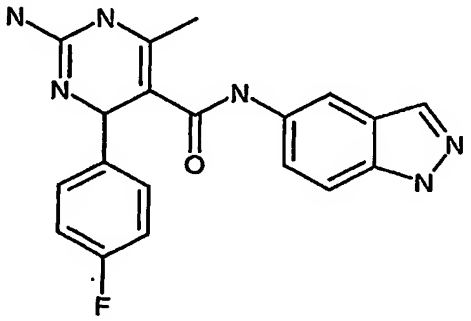
4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1-(phenylmethyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The title compound was synthesized using the procedure recited in Example 1(b), except N-benzylurea was used in place of urea, 1.0 equivalent of 4-fluorobenzaldehyde were used, and 0.05 equivalents of ytterbium triflate was used. The title compound was purified by RP-HPLC (retention time 8.69 min, 0-80% CH_3CN/H_2O/0.1% TFA over 10 minutes) to yield 37 mg (18%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 9.91 (s, 1H), 7.99-8.01 (m, 2H), 7.92 (d, 1H, 2.77Hz), 7.32-7.45 (m, 5H), 7.24-7.28 (m, 1H), 7.15-7.20 (m, 4H), 5.39 (s, 1H), 5.04 (d, 1H, 16.93Hz), 4.81 (d, 1H, 16.68Hz), 2.09 (s, 3H), 1.25 (s, 1H), 0.45-0.88 (m, 1H). MS (ES+) m/e 456 $[M+H]^+$.

Example 62

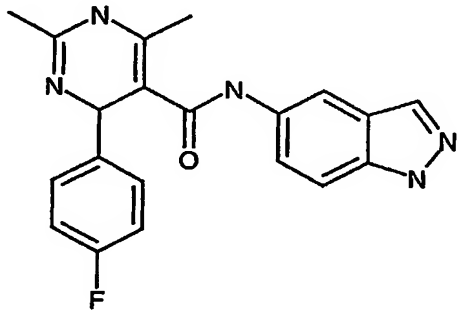
2-amino-4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide



(a) Preparation of title compound: Guanidine hydrochloride (48 mg, 1.2 equiv), p-fluorobenzaldehyde (52 mg, 1.0 equiv), *N*-1*H*-indazol-5-yl-3-oxobutanamide (Example 1(a), 100 mg, 1.1 equiv), and sodium bicarbonate (141 mg, 4.0 equiv) were combined in DMF (1 mL) and heated to 70°C in a sealed tube for three hours. The residue was poured onto ice (2 mL), diluted with ether (2 mL) and the product was collected by filtration. The solid was washed with water and ether and air dried. The title compound was purified further by RP-HPLC (retention time 5.99 min, 0-80% CH_3CN/H_2O/0.1% TFA over 10 minutes) to yield 9 mg (6%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 10.30 (s, 1H), 9.91 (s, 1H), 9.19 (s, 1H), 8.01 (s, 2H), 7.68 (s, 2H), 7.45 (d, 1H, 0.51Hz), 7.38-7.40 (m, 3H), 7.23-7.27 (m, 2H), 5.62 (s, 1H), 2.15 (s, 3H). MS (ES+) m/e 365 $[M+H]^+$.

Example 63

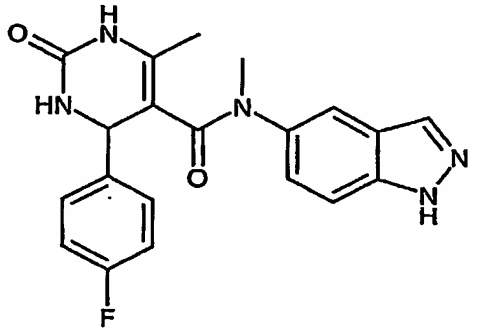
4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-2,6-dimethyl-1,4-dihydro-5-pyrimidinecarboxamide



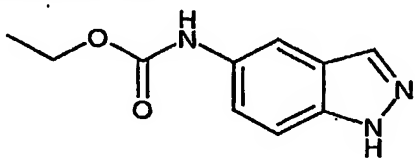
The title compound was synthesized using the procedure recited in Example 62 (a), except acetamidine hydrochloride was used in place of guanidine hydrochloride. The title compound was purified further by RP-HPLC (retention time 5.25 min, 0-80% CH_3CN/H_2O/0.1% TFA over 10 minutes) to yield 26 mg (17%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 11.26 (s, 1H), 11.07 (s, 1H), 9.99 (s, 1H), 8.01 (d, 1H, 1.01Hz), 7.96 (s, 1H), 7.45-7.53 (m, 3H), 7.26-7.33 (m, 3H), 5.86 (s, 1H), 2.30 (s, 3H), 2.12 (s, 3H). MS (ES+) m/e 364 $[M+H]^+$.

Example 64

4-(4-fluorophenyl)-N-1H-indazol-5-yl-N,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

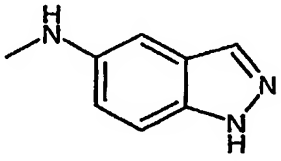


a) ethyl 1*H*-indazol-5-ylcarbamate



5-aminoindazole (3.0 g, 22.6 mmol, 1 equiv) was dissolved in pyridine (20 mL). The solution was cooled to 0 °C, and ethyl chloroformate (2.27 mL, 23.7 mmol, 1.05 equiv) was added. After 45 minutes, the reaction was quenched with water, and diluted with ethyl acetate. The layers were separated, and the organic layer was washed with 1N HCl (2x), satd. NaCl (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Trituration of the residue with CH_2Cl_2/hexanes afforded an off-white powder (1.19 g, 26%). 1H NMR (400 MHz, DMSO-D6) δ ppm 12.92 (s, 1H), 9.54 (s, 1H), 7.99 (s, 1H), 7.88 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.37 (dd, J = 1.8, 9.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 1H), 1.26 (t, J = 7.3 Hz, 1H) MS (ES+) m/e 206 $[M+H]^+$.

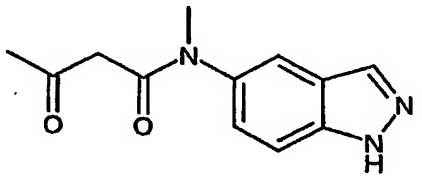
(b) *N*-methyl-1*H*-indazol-5-amine



The product of Example 50(a) (1.19g, 5.8 mmol, 1 equiv) was dissolved in THF (23 mL) and cooled to 0 °C. Lithium aluminum hydride (11.6 mL of a 1M solution in THF, 11.6 mmol, 2 equiv) was added slowly (gas evolved!) The reaction was warmed to room temperature over 20 minutes, then heated to reflux for 2.5 hours. The mixture was cooled to room temperature and quenched with a 1:1 mixture of

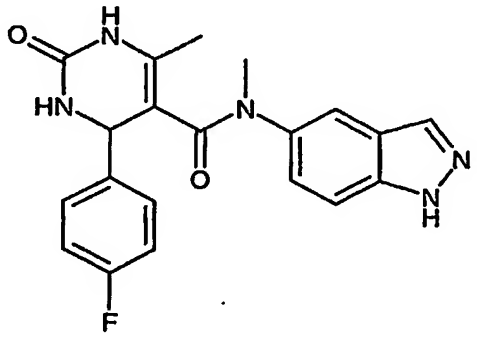
$Na_2SO_4 \cdot 12H_2O$:celite. The resulting slurry was filtered and the solids were washed with methanol. The product was purified by trituration with CH_2Cl_2/hexanes to provide the product as a white powdery solid (0.350 g, 41%). 1H NMR (400 MHz, DMSO-D6) δ ppm 12.57 (br s, 1H), 7.76 (d, J = 0.7 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 6.79 (dd, J = 2.3, 8.8 Hz, 1H), 6.56 (d, J = 1.7 Hz, 1H), 5.38 (q, J = 5.3 Hz, 1H), 2.69 (d, J = 5.3 Hz, 3H) MS (ES+) m/e 148 $[M+H]^+$.

(c) *N*-1*H*-indazol-5-yl-*N*-methyl-3-oxobutanamide



The product of Example 52(b) (350 mg, 2.38 mmol, 1 equiv) was dissolved in acetonitrile (1.5 mL). Diketene (0.183 mL, 2.38 mmol, 1 equiv) was added in a single portion. The reaction was sealed and heated to 50 °C for 2 hours. The mixture was cooled to room temperature and concentrated to a pale brown foam, which was sufficiently pure for use in the subsequent reaction (549 mg, 100%). 1H NMR (400 MHz, DMSO-D6) δ ppm 13.25 (br s, 1H), 8.12 (s, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 1.7, 8.5 Hz, 1H), 3.26 (s, 2H), 3.20 (s, 3H), 1.96 (s, 3H) MS (ES+) m/e 231 $[M+H]^+$.

(d) 4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-*N*,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

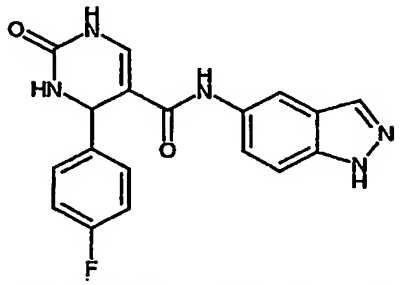


The title compound was synthesized using the procedure recited in Example 1(b), except *N*-1*H*-indazol-5-yl-*N*-methyl-3-oxobutanamide was utilized. 1H NMR (400 MHz, $CDCl_3$) δ ppm 13.25 (br s, 1H), 8.02 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.26 (m,

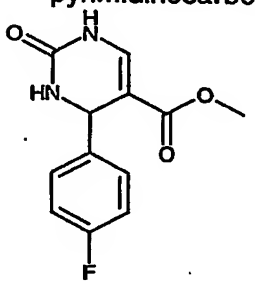
2H), 7.11 (t, J = 8.5 Hz, 2H), 7.05 (br s, 1H), 6.94 (dd, J = 1.7, 8.6 Hz, 1H), 6.07 (s, 1H), 5.09 (s, 1H), 4.93 (s, 1H), 3.24 (s, 3H), 1.90 (s, 3H) MS (ES+) m/e 380 $[M+H]^+$.

Example 65

4-(4-fluorophenyl)-N-1H-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

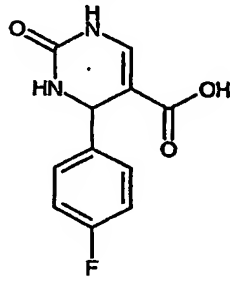


(b) methyl 4-(4-fluorophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate



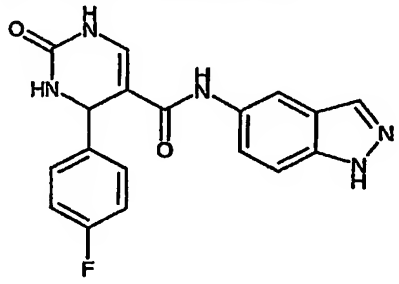
A round bottom flask was charged with 4-fluorobenzaldehyde (2.00 mL, 18.6 mmol, 1 equiv), methyl 3,3-dimethoxypropionate (2.49 mL, 18.6 mmol, 1 equiv), urea (1.68 g, 28.0 mmol, 1.5 equiv), and copper (I) chloride (184 mg, 1.86 mmol, 0.1 equiv). THF (18.6 mL) was added, followed by acetic acid (0.110 mL, 1.86 mmol, 0.1 equiv) and $BF_3 \cdot OEt_2$ (3.07 mL, 24.2 mmol, 1.3 equiv). The slurry was heated to reflux for 24 hours, then stirred at room temperature for an additional 36 hours. The mixture was diluted with water and carefully neutralized with satd. $NaHCO_3$. Ethyl acetate was added, and the biphasic solution was filtered through celite. The layers were separated, and the aqueous layer was washed with an additional portion of ethyl acetate. The combined organic extracts were washed with satd. NaCl, dried over Na_2SO_4, filtered and concentrated to a foamy solid. The residue was purified by flash chromatography (50% Ch_2Cl2/ethyl acetate) to provide 535 mg of the product as an off-white powder (535 mg, 11%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 9.25 (d, J = 5 Hz, 1H), 7.72 (br s, 1H), 7.30-7.26 (m, 3H), 7.17 (t, J = 8.9 Hz, 2H), 5.14 (d, J = 3 Hz, 1H), 3.56 (s, 3H) MS m/z 251 [M+H]+

(b) 4-(4-fluorophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid



The product of from Step A above (360 mg, 1.44 mmol, 1 equiv) was suspended in methanol (6.75 mL) and 2.5 M NaOH (2.25 mL) was added. The solution was heated to 60 °C for 6 hours, then cooled to room temperature and stirred for 18 hours. The reaction was diluted with ethyl acetate and water. The mixture was separated, and the pH of the aqueous layer was adjusted to 2 with 6N HCl. The acidified aqueous layer was extracted with ethyl acetate (2X). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was azeotroped several times with hexane to provide a pale yellow powder which was essentially pure (290 mg, 85%) NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 11.9 (br s, 1H), 9.11 (dd, J = 1.7, 5.8 Hz, 1H), 7.65 (br t, J = 2 Hz, 1H), 7.30 (dd, J = 5.6, 8.9 Hz, 2H), 7.23(d, J = 5.8 Hz, 1H), 7.18 (t, J = 8.8 Hz, 2H), 5.10 (d, J = 2.8 Hz, 1H), 1 MS m/z 236 [M+H]+

(c) 4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

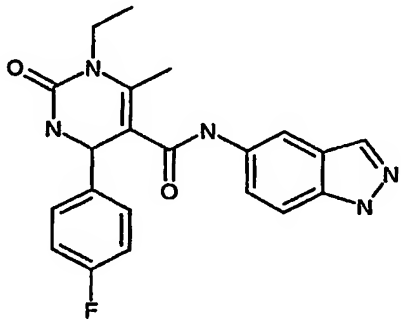


The product of Step b above (258 mg, 1.09 mmol, 1 equiv) was combined with 5-aminoindazole (303 mg, 2.28 mmol, 1.2 equiv) and EDC (437 mg, 2.28 mmol, 1.2 equiv) in a round bottom flask. DMF (4.5 mL) was added, followed by DMAP (30 mg) and triethylamine (0.318 mL, 2.28 mmol, 1.2 equiv). The reaction mixture was heated to 80 °C for 2 hours. The reaction was cooled to room temperature and poured into a separatory funnel containing ethyl acetate and water. The layers were

separated, and the organic layer was washed with 1M HCl (2x), satd. $NaHCO_3$ (1x), and satd. NaCl (1X). The organic extracts were dried over Na2SO4, filtered and concentrated to a yellow solid. One-fourth of the residue was further purified by reverse-phase HPLC (0-80% CH_3CN/H_2O/0.1%TFA over 10 minutes, retention time 6.26 min) to provide 9 mg of the product as a colorless solid. NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 12.92 (br s, 1H), 9.56 (s, 1H), 9.12 (dd, J = 1.6, 5.9 Hz, 1H), 8.04 (t, J = 1.3 Hz, 1H), 7.97 (s, 1H), 7.43 (d, J = 1.3 Hz, 2H), 7.40 (d, J = 5.8 Hz, 1H), 7.34 (m, 2H), 7.17 (t, J = 9.1 Hz, 2H), 5.45 (d, J = 3.1 Hz, 1H) MS m/z 352 [M+H]+

Example 66

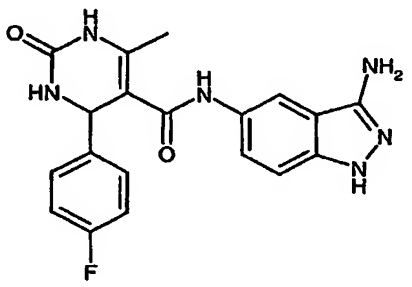
1-ethyl-4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



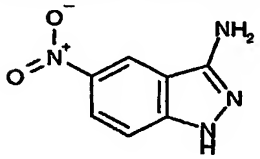
The title compound was synthesized using the procedure recited in Example 1(b), except 2.0 equivalents of N-ethylurea was used in place of urea, and 1.2 equivalents of p-fluorobenzaldehyde was used to yield 5 mg (3%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 12.97 (s, 1H), 9.83 (s, 1H), 8.02 (d, 2H, 18.7 Hz), 6.65 (d, 1H, 3.03 Hz), 7.39-7.46 (m, 2H), 7.29-7.32 (m, 1H), 7.15-7.19 (m, 2H), 6.54 (s, 1H), 5.27 (s, 1H), 3.76-3.81 (m, 1H), 3.52-3.55 (m, 1H), 2.19 (s, 3H), 1.11 (t, 3H, 6.82 Hz). MS (ES+) m/e 394 $[M+H]^+$.

Example 67

N-(3-amino-1H-indazol-5-yl)-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

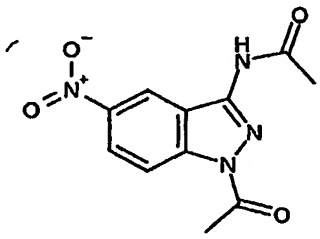


(a) 5-nitro-1*H*-indazol-3-amine



Hydrazine monohydrate (2.1 mL, 44 mmol) was added to a solution of 2-chloro-5-nitrobenzonitrile (7.30 g, 40 mmol) in pyridine (30 mL) and the mixture was heated to reflux overnight. The dark red solution was then cooled, poured into H_2O and the resulting solid filtered and dried to give the title compound as a dark red powder (5.7 g, 80%). NMR 1H NMR (400 MHz, DMSO-D6) δ ppm 8.95 (d, J = 2.0, 1H), 8.06 (dd, J = 9.2, 2.0, 1H), 7.34 (d, J = 9.2, 1H), 5.98 (br s, 2H) MS m/z 179.0 [M+H]+

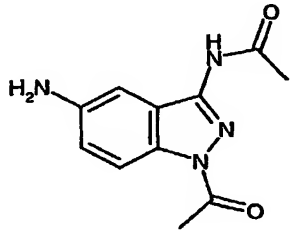
(b) *N*-(1-acetyl-5-nitro-1*H*-indazol-3-yl)acetamide



The product from Step A above (3.6 g, 20.2 mmol) was dissolved in pyridine (30 mL), acetic anhydride (4.15 mL, 44 mmol) was added and the mixture was stirred overnight at rt. The red solution was pouted into H_2O and the resulting solid was filtered to give the title compunt as a red solid (4.8 g, 91%). NMR 1H NMR (400 MHz,

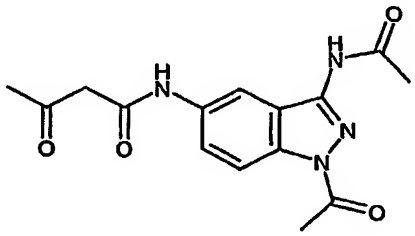
DMSO-D6) δ 11.21 (br s, 1H), 9.08 (s, 1H), 8.46 (s, 2H), 2.51 (s, 3H), 2.23 (s, 3H) (MS m/z 263.2.0 [M+H]+

(c) *N*-(1-acetyl-5-amino-1*H*-indazol-3-yl)acetamide



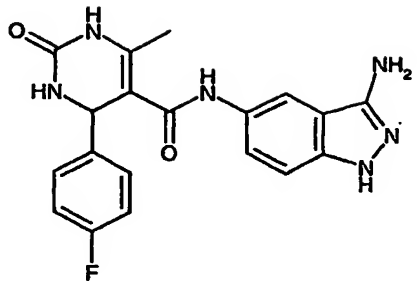
The product from Step B above (3.0 g, 11.4 mmol) and 5% Pd/C (1 g) were combined in MeOH (40 mL) and hydrogenated uner a balloon of H_2 for 3 h. The mixture was filtered through Celite and the filtrate was concentrated to give the title compound as a dark solid (2.6 g, 98%). NMR 1H NMR (400 MHz, DMSO-D6) δ 10.62 (s, 1H), 7.97 (dd, J = 7.9, 1.8, 1H), 6.93-6.89 (m, 2H), 5.26 (s, 2H), 2.52 (s, 3H), 2.08 (s, 3H) (MS m/z 233.2 [M+H]+

(d) *N*-[1-acetyl-3-(acetylamino)-1*H*-indazol-5-yl]-3-oxobutanamide



The product from Step C above (2.6 g, 11.4 mmol) was dissolved in acetonitrile (20 mL) and diketene (0.86 mL, 11.2 mmol) was added in portions over 10 min, then the solution was sealed and heated to 50 °C overnight. The reaction mixture was then cooled, fitlered and the filtrate was concentrated to give the title compound as a dark tan solid (2.6 g, 73%). NMR 1H NMR (400 MHz, DMSO-D6) δ 10.86 (s, 1H), 10.32 (s, 1H), 8.25-8.20 (m, 2H), 7.75 (dd, J = 8.9, 2.0, 1H), 3.59 (s, 2H), 2.63 (s, 3H), 2.22 (s, 3H), 3.18 (s, 3H) MS m/z 317.0 [M+H]+

(d) *N*-(3-amino-1*H*-indazol-5-yl)-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide



The product from Step D above (1.35 g, 4.2 mmol) was treated as in Example 1b, Method B, except that heating was continued overnight. The reaction mixture was concentrated to give a mixture of bis-acetyl and mono-acetyl. The crude solid was dissolved in THF (15 mL) and 6M aq. HCl (5 mL) was added and the mixture was heated to reflux for 3 h. The reaction mixture was cooled, concentrated and the residue poured into sat. aq. K_2CO_3 and extracted with EtOAc/THF. The organic extracts were washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated to give a solid, a portion of which was purified by reverse-phase HPLC to give the title compound as a tan solid. (NMR 1H NMR (400 MHz, MeOD) δ (8.28 (s, 1H), 7.53 (dd, J = 9.1, 2.0), 7.43-7.39 (m, 3H), 7.11-7.06 (m, 3H), 5.54 (s, 1H), 3.33 (s, 3H), MS m/z 381.3 [M+H]+

BIOLOGICAL DATA

ROCK kinase assay:

ROCK inhibitor activity was determined using human recombinant ROCK1 kinase domain (amino acid 2-543) expressed in Sf9 cells (see WO9967283). The enzyme was purified using His-tag NTA column and Source15 HPLC chromatography. The assay of Rock-1 activity involved incubation with peptide substrate and ATP^{33}, the subsequent incorporation of P^{33} into the peptide was quantified by Scintillation Proximity Assay (SPA - Amersham Pharmacia).

For IC50 determination, test compounds were typically dissolved at 10mM in 100% DMSO, with subsequent serial dilution in 100% DMSO. Compounds were typically assayed over an eleven point dilution range with a concentration in the assay of 50uM to 0.8nM, in 3-fold dilutions. IC50 values were calculated by bespoke curve fitting software and then converted to pIC50.

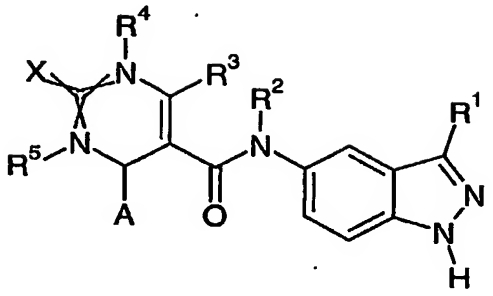
Assays were performed in opaque, white walled, 384 well plates, in a total assay volume of 20ul. The assays contained: 1nM hROCK1; 1uM biotinylated peptide (biotin-Ahx-AKRRRLSSLRA-CONH2); 1uM ATP; 1.85kBq per well ATP(γ-33P); 25mM Hepes pH 7.4; 15mM $MgCl_2$; 0.015% BSA. The reactions were incubated at 22°C for 120 minutes, then terminated by the addition of a 50ul solution containing 60mM EDTA and streptavidin PVT SPA beads. The SPA beads were added to a concentration of 0.14mg per well. The plates were allowed to incubate at 22°C for 10 minutes before centrifugation at 1500 rpm for 1 minute. P^{33} incorporation was quantified by scintillation counting in a Packard TopCount.

All exemplified Examples 1-67 were run with the recited assay and showed inhibitory activity versus Rock-1 with a pIC_{50} of 5.0 or greater.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

 indicates a single or double bond;

X is =O, =S, C_1-C_3 alkyl, or -N(H)R;

A is aryl, aralkyl, heteroaryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl;

R is C_1-C_3 alkyl, aryl, heteroaryl, -C(O)R", -$S(O)_2$R", or -C(O)NR";

R^1 is –H, halo, C_1-C_6 alkyl, aryl, heteroaryl, or N(H)R';

R' is –H, C_1-C_3 alkyl, aryl, -C(O)R", -S(O)2R", or -C(O)N(H)R";

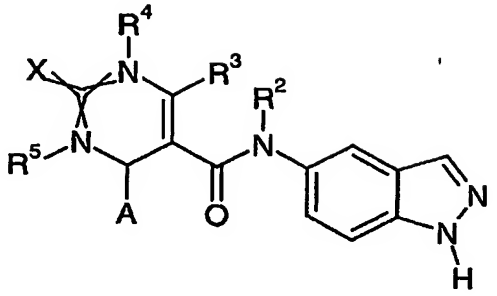
R" is C_1-C_3 alkyl;

R^2 is –H or C_1-C_3 alkyl;

R^3 is -H, C_1-C_3 alkyl, aryl or heteroaryl; and

R^4 and R^5 are each independently –H, C_1-C_3 alkyl or aralkyl.

2. A compound of Formula (I'):



(I')

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

⁄ indicates a single or double bond;

X is =O, =S, C_1-C_3 alkyl, or -N(H)R;

A is aryl, aralkyl, heteroaryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl;

R is C_1-C_3 alkyl, aryl, heteroaryl, -C(O)R", -$S(O)_2$R", or -C(O)NR";

R' is –H, C_1-C_3 alkyl, aryl, -C(O)R", -S(O)2R", or -C(O)N(H)R";

R" is C_1-C_3 alkyl;

R^2 is –H or C_1-C_3 alkyl;

R^3 is -H, C_1-C_3 alkyl, aryl or heteroaryl; and

R^4 and R^5 are each independently –H, C_1-C_3 alkyl or aralkyl.

3. A compound as claimed in claim 1 selected from the group:

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3,4-bis(ethyloxy)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-[4-(methylsulfonyl)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(3-thienyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-4,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(1-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(2-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-{5-[(1*H*-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoic acid;

4-(2,4-difluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-[3-(methyloxy)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-[2-(methyloxy)phenyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-cyanophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

3-{5-[(1*H*-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoic acid;

4-(2-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-chloro-4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-{3-[(2-hydroxyethyl)oxy]phenyl}-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

4-(4-bromo-2-thienyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-hydroxyphenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-chloro-2-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-{3-[(methylsulfonyl)amino]phenyl}-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(6-quinoxalinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide

4-[4-(aminosulfonyl)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(2-quinolinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3-fluoro-4-(methyloxy)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-cyanophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(1*H*-imidazol-1-yl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-(3-quinolinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-[(*E*)-2-phenylethenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-2-oxo-4-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-chlorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[4-(acetylamino)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(2-chlorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(2,3-dihydro-1,4-benzodioxin-6-yl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-hydroxyphenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(8-hydroxy-2-quinolinyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3,4-bis(methyloxy)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[2-(4-chlorophenyl)ethyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[3-(1*H*-imidazol-1-yl)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-chlorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[4-(aminocarbonyl)phenyl]-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-(1-methylethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-6-(2-furanyl)-*N*-1*H*-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-1,6-dimethyl-4-(2-naphthalenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(2-naphthalenyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-thioxo-1,2;3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1*H*-indazol-5-yl-6-methyl-4-(3-thienyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-2-oxo-1-(phenylmethyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

2-amino-4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-2,6-dimethyl-1,4-dihydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-*N*-1*H*-indazol-5-yl-*N*,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluorophenyl)-N-1H-indazol-5-yl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

1-ethyl-4-(4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide; and

N-(3-amino-1H-indazol-5-yl)-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

or a salt, solvate, or physiologically functional derivative thereof.

4. A compound as claimed in claim 1 selected from the group:

N-1H-indazol-5-yl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-2-oxo-4-(4-pyridinyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

Methyl 3-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoate;

Methyl 4-{5-[(1H-indazol-5-ylamino)carbonyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-4-pyrimidinyl}benzoate;

4-(3-furanyl)-*N*-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-4-(2-methylpropyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-2-oxo-4-(2-phenylethyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

N-1H-indazol-5-yl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(3-cyano-4-fluorophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-(4-fluoro-3-nitrophenyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

4-[2-hydroxy-4-(methyloxy)phenyl]-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide; and

4-(4-biphenylyl)-N-1H-indazol-5-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide;

or a salt, solvate, or physiologically functional derivative thereof.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

6. A method of treating a disorder in a mammal, said disorder being mediated by inappropriate ROCK-1 activity, comprising: administering to said mammal a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5, or a salt, solvate or a physiologically functional derivative thereof.

7. A compound as claimed in any one of claims 1 to 5, or a salt, solvate, or a physiologically functional derivative thereof for use in therapy.

8. Use of a compound as claimed in any one of claims 1 to 5, or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate ROCK-1 activity.

ABSTRACT

The present invention relates to indazolo-tetrahydropyrimidine-carboxamide derivatives, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such indazolo-tetrahydropyrimidine-carboxamide derivatives are useful in the treatment of diseases associated with inappropriate ROCK-1 kinase.